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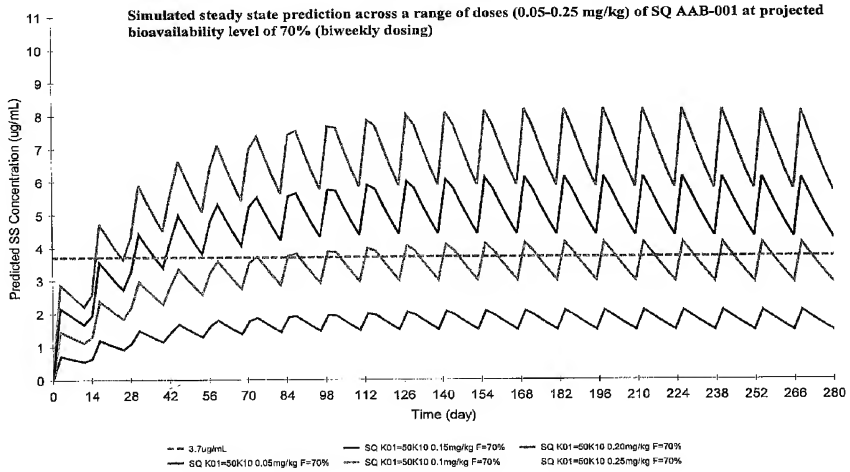
(54) **Title**: TREATMENT OF AMYLOIDOGENIC DISEASES

Figure 6



(57) **Abstract**: The invention provides preferred dosage ranges, maximum concentrations, average concentrations and monitoring regimes for use in treatment of Alzheimer's disease using antibodies to Aß. The invention also provides monitoring regimes that can assess changes in symptoms or signs of the patient following treatment.

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TREATMENT OF AMYLOIDOGENIC DISEASES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of International Application No. PCT/US07/09499 filed April 18, 2007 which claims the benefit under 35 U.S.C. § 119(e) of US Application No. 60/793014 filed April 18, 2006, each of which is incorporated by reference in their entirety for all purposes.

Background of the Invention

[0001] Alzheimer's disease (AD) is a progressive disease resulting in senile dementia. *See generally* Selkoe, *TINS* 16:403 (1993); Hardy *et al.*, WO 92/13069; Selkoe, *J. Neuropathol. Exp. Neurol.* 53:438 (1994); Duff *et al.*, *Nature* 373:476 (1995); Games *et al.*, *Nature* 373:523 (1995). Broadly speaking, the disease falls into two categories: late onset, which occurs in old age (65 + years) and early onset, which develops well before the senile period, *i.e.*, between 35 and 60 years. In both types of disease, the pathology is the same but the abnormalities tend to be more severe and widespread in cases beginning at an earlier age. The disease is characterized by at least two types of lesions in the brain, neurofibrillary tangles and senile plaques. Neurofibrillary tangles are intracellular deposits of microtubule associated tau protein consisting of two filaments twisted about each other in pairs. Senile plaques (*i.e.*, amyloid plaques) are areas of disorganized neuropil up to 150 μm across with extracellular amyloid deposits at the center which are visible by microscopic analysis of sections of brain tissue. The accumulation of amyloid plaques within the brain is also associated with Down's syndrome and other cognitive disorders.

[0002] The principal constituent of the plaques is a peptide termed Aβ or β-amyloid peptide. Aβ peptide is a 4-kDa internal fragment of 39-43 amino acids of a larger transmembrane glycoprotein named protein termed amyloid precursor protein (APP). As a result of proteolytic processing of APP by different secretase enzymes, Aβ is primarily found in both a short form, 40 amino acids in length, and a long form, ranging from 42-43 amino acids in length. Part of the hydrophobic transmembrane domain of APP is found at the carboxy end of Aβ, and may account for the ability of Aβ to aggregate into plaques, particularly in the case of the long form. Accumulation of amyloid plaques in the brain eventually leads to neuronal cell death. The physical symptoms associated with this type of neural deterioration characterize Alzheimer's disease.

[0003] Several mutations within the APP protein have been correlated with the presence of Alzheimer's disease. See, *e.g.*, Goate *et al.*, *Nature* 349:704 (1991) (valine^{717} to isoleucine); Chartier Harlan *et al. Nature* 353:844 (1991)) (valine^{717} to glycine); Murrell *et al.*, *Science* 254:97 (1991) (valine^{717} to phenylalanine); Mullan *et al.*, *Nature Genet.* 1:345 (1992) (a double mutation changing lysine^{595}-methionine^{596} to asparagine^{595}-leucine^{596}). Such mutations are thought to cause Alzheimer's disease by increased or altered processing of APP to Aβ, particularly processing of APP to increased amounts of the long form of Aβ (*i.e.*, Aβ1-42 and Aβ1-43). Mutations in other genes, such as the presenilin genes, PS1 and PS2, are thought indirectly to affect processing of APP to generate increased amounts of long form Aβ (see Hardy, *TINS* 20: 154 (1997)).

[0004] Mouse models have been used successfully to determine the significance of amyloid plaques in Alzheimer's (Games *et al.*, *supra*, Johnson-Wood *et al.*, *Proc. Natl. Acad. Sci. USA* 94:1550 (1997)). In particular, when PDAPP transgenic mice, (which express a mutant form of human APP and develop Alzheimer's disease at a young age), are injected with the long form of Aβ, they display both a decrease in the progression of Alzheimer's and an increase in antibody titers to the Aβ peptide (Schenk *et al.*, *Nature* 400, 173 (1999)). The observations discussed above indicate that Aβ, particularly in its long form, is a causative element in Alzheimer's disease.

[0005] McMichael, EP 526,511, proposes administration of homeopathic dosages (less than or equal to 10^{-2} mg/day) of Aβ to patients with preestablished AD. In a typical human with about 5 liters of plasma, even the upper limit of this dosage would be expected to generate a concentration of no more than 2 pg/ml. The normal concentration of Aβ in human plasma is typically in the range of 50-200 pg/ml (Seubert *et al.*, *Nature* 359:325 (1992)). Because EP 526,511's proposed dosage would barely alter the level of endogenous circulating Aβ and because EP 526,511 does not recommend use of an adjuvant, as an immunostimulant, it seems implausible that any therapeutic benefit would result.

[0006] Accordingly, there exists the need for new therapies and reagents for the treatment of Alzheimer's disease, in particular, therapies and reagents capable of effecting a therapeutic benefit at physiologic (*e.g.*, non-toxic) doses.

Cross-Reference to Related Applications

[0007] U.S. Application No. 60/648,631 filed on January 28, 2005; U.S. Publication No. US 20060193850 A1 published on August 31, 2006; International Publication No. WO 06/083689 published on August 10, 2006; U.S. Application No. 60/622,525 filed on October 26, 2004 and, U.S. Publication No. US 20060160161 A1 published on July 20, 2006 are related applications, all of which are incorporated by herein reference in their entirety for all purposes.

Summary of the Invention

[0008] The invention provides methods of therapeutically treating Alzheimer's disease. The methods comprise administering by intravenous infusion to a patient suffering from the disease a dosage of an antibody within a range of about 0.5 mg/kg to less than 5 mg/kg. The antibody specifically binds to an N-terminal fragment of beta amyloid peptide (Aβ) with a binding affinity of at least 10^7 M^{-1}, and thereby therapeutically treats the patient. Optionally, the antibody is a humanized antibody. Optionally, the humanized antibody is a humanized version of mouse antibody 3D6 expressed by the hybridoma deposited under ATCC under No. PTA-5130. Optionally, the humanized antibody comprises (i) a light chain comprising three complementarity determining regions (CDRs) from the immunological light chain variable region of the mouse antibody 3D6; and (ii) a heavy chain comprising three complementarity determining regions (CDRs) from the immunological heavy chain variable region of mouse antibody 3D6. Optionally, the humanized antibody comprises (i) a variable light chain region having the sequence as set forth in SEQ ID NO:1, SEQ ID NO:3 or SEQ ID NO:5; and (ii) a variable heavy chain region having the sequence as set forth in SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6. Optionally, the humanized antibody comprises (i) a variable light chain region having the sequence as set forth in SEQ ID NO:1 or SEQ ID NO:5; and (ii) a variable heavy chain region having the sequence as set forth in SEQ ID NO:2 or SEQ ID NO:6. Optionally, the humanized antibody is bapineuzumab. Optionally, the antibody is a humanized version of mouse antibody 10D5 expressed by the hybridoma deposited under ATCC under No. PTA-5129. Optionally, the humanized antibody comprises (i) a light chain comprising three complementarity determining regions (CDRs) from the immunological light chain variable region of the mouse antibody 10D5; and (ii) a heavy chain comprising three complementarity determining regions (CDRs) from the

immunological heavy chain variable region of mouse antibody 10D5. Optionally, the humanized antibody comprises (i) a variable light chain region having the sequence as set forth in SEQ ID NO:7 or SEQ ID NO: 28 as set forth in US Patent Publication No. 20050142131; and (ii) a variable heavy chain region having the sequence as set forth in SEQ ID NO:8 or SEQ ID NO: 29 as set forth in US Patent Publication No. 20050142131. Optionally, the humanized antibody is a humanized version of mouse antibody 12A11 expressed by the hybridoma deposited under with the American Type Culture Collection (ATCC), Manassas, VA 20108, USA on April 8, 2003 under the terms of the Budapest Treaty and has deposit number PTA-7271.

[0009] Optionally, the humanized antibody comprises (i) a light chain comprising three complementarity determining regions (CDRs) from the immunological light chain variable region of the mouse antibody 12A11; and (ii) a heavy chain comprising three complementarity determining regions (CDRs) from the immunological heavy chain variable region of mouse antibody 12A11. Optionally, the humanized antibody comprises (i) a variable light chain region having the sequence as set forth in SEQ ID NO:2 as set forth in US Patent Publication No. 20050118651; and (ii) a variable heavy chain region having the sequence as set forth in SEQ ID NO:4 as set forth in US Patent Publication No. 20050118651.In some methods, the dosage is about 0.5 mg/kg. In some methods, the dosage is about 1.5 mg/kg. In some methods, the dosage is 0.5 to 3 mg/kg. In some methods, the dosage is 0.5 to 1.5 mg/kg. In some methods, the dosage is administered on multiple occasions, such as every 13 weeks.

[0010] Some methods further comprise monitoring the patient by at least one type of assessment selected from the group of consisting of Mini-Mental State Exam (MMSE), Alzheimer's Disease Assessment Scale - cognitive (ADAS-COG), Clinician Interview-Based Impression (CIBI), Neurological Test Battery (NTB), Disability Assessment for Dementia (DAD), Clinical Dementia Rating-sum of boxes (CDR-SOB), Neuropsychiatric Inventory (NPI), Positron Emission Tomography (PET Imaging) scan, Magnetic Resonance Imaging (MRI) scan, and measurement of blood pressure. In some methods, the type of assessment is an MMSE, and the MMSE is administered on multiple occasions, such as before administering the dosage, and at week 4, week 16, 6 months, and 1 year after administering the dosage. In some methods, the MMSE score measured after administration is higher than a previously assessed MMSE score.

[0011] The invention further provides methods of therapeutically treating Alzheimer's disease, comprising administering by intravenous infusion to a patient suffering from the disease a dosage of an antibody within a range of about 0.5 mg/kg to less than 5 mg/kg, wherein the antibody specifically binds to beta amyloid peptide (Aβ) with a binding affinity of at least 10^7 M^{-1}, and monitoring the patient for posterior reversible encephalopathy syndrome (PRES) or vascular edema. Optionally, the monitoring comprises performing an MRI scan, optionally with a FLAIR (Fluid Attenuated Inversion Recovery) sequence imaging. In some methods, the monitoring identifies of at least one clinical symptom associated with PRES, such as headache, nausea, vomiting, confusion, seizures, visual abnormalities, altered mental functioning, ataxia, frontal symptoms, parietal symptoms, stupor, or focal neurological signs. In some methods, the dosage is reduced or suspended based on an outcome of the MRI scan that is indicative of PRES or vascular edema. In some methods, the dosage is reduced or suspended based on an outcome of the FLAIR sequence imaging that is indicative of PRES or vascular edema. In some methods, the dosage is reduced or suspended based on an identification of at least one clinical symptom associated with PRES. In some methods, the MRI scan is every 3 months, every 6 months, or every year. In some methods, the FLAIR sequence imaging is every 3 months, every 6 months, or every year.

[0012] Some of the above methods further comprise determining presence or absence of hypertension in the patient, wherein if the patient has hypertension, the method further comprises administering an antihypertensive. Optionally, the antihypertensive is selected from the group consisting of hydroclorothiazide, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II-receptor blockers (ARB), beta blockers, and calcium channel blockers.

[0013] Some methods further comprise administering a steroid to the patient to treat the PRES or vascular edema. Optionally, the steroid is dexamethasone or methyprednisolone.

[0014] Some methods further comprise reducing or suspending the dosage based on an outcome of the MRI scan and that is indicative of PRES or vascular and identifying at least one clinical symptom associated with PRES or vascular edema, such as headache, nausea, vomiting, confusion, seizures, visual abnormalities, altered mental functioning, ataxia, frontal symptoms, parietal symptoms, stupor, or focal neurological signs. Some methods further comprise reducing or suspending the dosage based on an outcome of the

FLAIR sequence imaging that is indicative of PRES or vascular edema and identifying of at least one clinical symptom associated with PRES or vascular edema, such as headache, nausea, vomiting, confusion, seizures, visual abnormalities, altered mental functioning, ataxia, frontal symptoms, parietal symptoms, stupor, or focal neurological signs.

[0015] In some methods, the monitoring indicates presence of PRES or vascular edema at a first time point after administration, and absence of PRES or vascular edema at a second time point after the first point, and the patient is administered a first dosage before the monitoring indicates presence of PRES or vascular edema, a second dosage or no dosage after the monitoring detects presence of PRES or vascular edema, and a third dosage after the monitoring detects absence of PRES or vascular edema, wherein the first and third dosage are higher than the second dosage.

[0016] In some of the above methods, the antibody is a humanized antibody. Optionally, the humanized antibody is a humanized version of mouse antibody 3D6 expressed by the hybridoma deposited with the American Type Culture Collection (ATCC), Manassas, VA 20108, USA on April 8, 2003 under the terms of the Budapest Treaty and has deposit number PTA-5130.

[0017] Optionally, the humanized antibody comprises (i) a light chain comprising three complementarity determining regions (CDRs) from the immunological light chain variable region of the mouse antibody 3D6; and (ii) a heavy chain comprising three complementarity determining regions (CDRs) from the immunological heavy chain variable region of mouse antibody 3D6. Optionally, the humanized antibody comprises (i) a variable light chain region having the sequence as set forth in SEQ ID NO:1, SEQ ID NO:3 or SEQ ID NO:5; and (ii) a variable heavy chain region having the sequence as set forth in SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6. Optionally, the humanized antibody comprises (i) a variable light chain region having the sequence as set forth in SEQ ID NO:1 or SEQ ID NO:5; and (ii) a variable heavy chain region having the sequence as set forth in SEQ ID NO:2 or SEQ ID NO:6. Optionally, the humanized antibody is bapineuzumab.

[0018] In some of the above methods, the dosage is about 0.5 mg/kg. In some methods, the dosage is about 1.5 mg/kg. In some methods, the dosage is 0.5 to 3 mg/kg. In some methods, the dosage is 0.5 to 1.5 mg/kg. In some methods, the dosage is administered on multiple occasions, such as every 13 weeks.

[0019] In some of the above methods, Bapineuzumab is administered at a first dosage before PRES or vascular edema is determined from the MRI scan and a second dosage after PRES or vascular edema is determined from the MRI scan, and the second dosage is less then

the first dosage. Optionally, the first dosage is 3-5 mg/kg and the second dosage is 0.5 to 3 mg/kg. Optionally, the second dosage is half of the first dosage. Optionally, the Bapineuzumab is administered at a first frequency before the MRI shows PRES or vascular edema and a second frequency after the MRI shows PRES or vascular edema, and the second frequency is less than the first frequency.

[0020] In some of the above methods, the type of assessment is blood pressure, and the presence or absence of hypertension is determined. Optionally, if the patient has hypertension, the method further comprises administering an antihypertensive. Optionally, the antihypertensive is selected from the group consisting of hydroclorothiazide, Angiotensin-converting Enzyme (ACE) Inhibitors, angiotensin II-receptor blockers (ARB), beta blockers, and calcium channel blockers.

[0021] The invention further provides therapeutic products. The products comprise a glass vial and instructions. The glass vial contains a formulation comprising about 10 mg to about 250 mg of a humanized anti Aβ antibody, about 4% mannitol or about 150 mM NaCl, about 5 mM to about 10 mM histidine, and about 10 mM methionine. The instructions to monitor a patient to whom the formulation is administered for PRES and or vascular edema are included with the products.

[0022] The invention provides methods method of treating Alzheimer disease comprising subcutaneously administering to a patient having the disease an antibody that specifically binds to an N-terminal fragment of Aβ, wherein the antibody is administered at a dose of 0.01-0.6 mg/kg and a frequency of between weekly and monthly. Optionally, the antibody is administered at a dose of 0.05-0.5 mg/kg. Optionally, the antibody is administered at a dose of 0.05-0.25 mg/kg. Optionally, the antibody is administered at a dose of 0.015-0.2 mg/kg weekly to biweekly. Optionally, the antibody is administered at a dose of 0.05-0.15 mg/kg weekly to biweekly. Optionally, the antibody is administered at a dose of 0.05-0.07 mg/kg weekly. Optionally, the antibody is administered at a dose of 0.06 mg/kg weekly. Optionally, the antibody is administered at a dose of 0.1 to 0.15 mg/kg biweekly. Optionally, the antibody is administered at a dose of 0.1 to 0.3 mg/kg monthly. Optionally, the antibody is administered at a dose of 0.2 mg/kg monthly.

[0023] The invention provides methods of treating Alzheimer disease comprising subcutaneously administering to a patient having the disease an antibody that specifically binds to an N-terminal fragment of Aβ, wherein the antibody is administered at a dose of 1-40 mg and a frequency of between weekly and monthly. Optionally, the antibody is

administered at a dose of 5-25 mg. Optionally, the antibody is administered at a dose of 2.5-15 mg. Optionally, the antibody is administered at a dose of 1-12 mg weekly to biweekly. Optionally, the antibody is administered at a dose of 2.5-10 mg weekly to biweekly. Optionally, the antibody is administered at a dose of 2.5-5 mg weekly. Optionally, the antibody is administered at a dose of 4-5 mg weekly. Optionally, the antibody is administered at a dose of 7-10 mg biweekly.

[0024] The invention provides methods of treating Alzheimer disease, comprising administering to a patient having the disease an antibody that specifically binds to an N-terminal fragment of Aβ in a regime sufficient to maintain a maximum serum concentration of the antibody in the patient less than about 28 μg antibody/ml serum and thereby treating the patient. Optionally, the maximum serum concentration is within a range of about 4-28 μg antibody/ml serum. Optionally, the maximum serum concentration is within a range of about 4-18 μg antibody/ml serum. Optionally, the average serum concentration of the antibody in the patient is below about 7 μg antibody/ml serum. Optionally, the average serum concentration is within a range of about 2-7 μg antibody/ml serum. Optionally, the average serum concentration is about 5 μg antibody/ml serum. Optionally, the antibody is administered intravenously. Optionally, the antibody is administered subcutaneously. Optionally, a dose of 0.1-1.0 mg/kg is administered monthly. Optionally, a dose of 0.5-1.0 mg/kg is administered monthly. Optionally, the antibody is administered at a frequency between weekly and monthly. Optionally, the antibody is administered weekly or biweekly. Some methods further comprise measuring the concentration of antibody in the serum and adjusting the regime if the measured concentration falls outside the range. Optionally, the antibody is a humanized antibody. Optionally, the humanized antibody is a humanized version of mouse antibody 3D6 expressed by the hybridoma deposited under ATCC under No. PTA-5130. Optionally, the humanized antibody is bapineuzumab. Optionally, the humanized antibody is a humanized version of mouse antibody 10D5 expressed by the hybridoma deposited under ATCC under No. PTA-5129. Optionally, the humanized antibody is a humanized version of mouse antibody 12A11 expressed by the hybridoma deposited under ATCC under No. PTA-7271.

[0025] The invention provides methods of treating Alzheimer disease, comprising administering to a patient having the disease an antibody that specifically binds to an N-terminal fragment of Aβ in a regime sufficient to maintain an average serum concentration of the antibody in the patient below about 7 μg antibody/ml serum and thereby treat the patient.

Optionally, the average serum concentration is within a range of about 2-7 μg antibody/ml serum. Optionally, the average serum concentration is about 5 μg antibody/ml serum. Optionally, the antibody is administered intravenously. Optionally, the antibody is administered subcutaneously. Optionally, a dose of 0.1-1.0 mg/kg is administered monthly. Optionally, a dose of 0.5-1.0 mg/kg is administered monthly. Optionally, the antibody is administered at a frequency between weekly and monthly. Optionally, the antibody is administered weekly or biweekly. Some methods further comprise measuring the concentration of antibody in the serum and adjusting the regime if the measured concentration falls outside the range. Optionally, the antibody is a humanized antibody. Optionally, the humanized antibody is a humanized version of mouse antibody 3D6 expressed by the hybridoma deposited under ATCC under No. PTA-5130. Optionally, the humanized antibody is bapineuzumab. Optionally, the humanized antibody is a humanized version of mouse antibody 10D5 expressed by the hybridoma deposited under ATCC under No. PTA-5129. Optionally, the humanized antibody is a humanized version of mouse antibody 12A11 expressed by the hybridoma deposited under ATCC under No. PTA-7271.

Brief Description of the Drawings

[0026] Figure 1 shows light (SEQ ID NO: 30) and heavy chain (SEQ ID NO: 31) amino acid sequence of Bapineuzumab predicted from the expression construct DNA sequences.

[0027] Figure 2 shows the average MMSE change from baseline.

[0028] Figure 3 shows the change from baseline MMSE by cohort at month 4.

[0029] Figure 4 shows the mean, median and standard deviation MMSE change from baseline at month four.

[0030] Figure 5 shows the results of statistical testing of the MMSE change from baseline at month four.

[0031] Figure 6 shows simulated steady state serum concentrations of antibody from various subcutaneous regimes assuming bioavailability of 70%.

[0032] Figure 7 shows steady state concentrations of antibody following subcutaneous administration of AAB-001 at doses of 0.05 or 0.06 mg/kg assuming 70% or 100% bioavailability.

[0033] Figure 8 shows plasma Aβ levels following administration of AAB-001 at doses of 0.15, 0.5, or 1.0 mg/kg.

[0034] Figure 9 shows pharmacokinetic parameters following intravenous administration of AAB-001 at doses of 0.15, 0.5, 1.0, and 2.0 mg/kg.

[0035] Figure 10 shows the mean serum AAB-001 concentration vs. time profiles following intravenous administration of AAB-001 at doses of 0.15, 0.5, 1.0, and 2.0 mg/kg.

[0036] Figure 11 shows plasma Aβ levels following intravenous administration of AAB-001 at doses of 0.15, 0.5, and 1.0 mg/kg.

Detailed Description of the Invention

[0037] The application provides preferred dosages and frequencies of administration of antibodies to an N-terminal fragment of Aβ to maximize therapeutic benefit relative to occurrence of side effects, particularly vasogenic edema. A series of experiments using different regimes of the mouse 3D6 antibody in transgenic PDAPP mouse have identified a steady state average serum concentration of antibody of about 3.7 μg/ml for reducing amyloid accumulation. The present data provide evidence that doses of 0.5 mg/kg and 1.5 mg/kg administered intravenously every 13 weeks were effective in inhibiting cognitive decline in Alzheimer's patients. These regimes give rise to average serum concentrations of antibody that bracket the effective dose of 3.7 μg/ml in mice. For example, a dose of 0.5 mg/kg administered every 13 weeks was found to give an average serum concentration of about 3 μg/ml. A dose of 1 mg/kg administered every 13 weeks was found to give an average serum concentration of about 5.5 μg/ml and a dose of 2 mg/kg administered every 13 weeks was predicted to give an average serum concentration of 9.4 μg/ml. Thus, the present data indicate that the same order of magnitude of serum concentrations of antibody that are effective in mice are effective in humans. These data are further supported by clinical trials using immunotherapy with full-length Aβ1-42. In these trials, antibody responders were found to have a statistically significant inhibition of cognitive decline. The antibody responders had an ELISA titer of antibody of at least 1 in 2200, which corresponds to a serum titer of about 1 μg/ml.

[0038] The present data also provide evidence that higher doses of antibody particularly 5 mg/kg achieve no greater (and possibly less) therapeutic benefit than lower doses in the 0.5-1.5 mg/kg range but also produce significant side effects, particularly vasogenic edema, in some patients. Although practice of the present invention is not dependent on an understanding of mechanism, it is believed that the side effects result from high maximum concentrations of antibody following its administration.

[0039] In the aggregate, these data indicate that therapeutic benefit can be obtained with relatively modest doses of antibody designed to give similar average serum concentrations to the 3.7 μg/ml found effective in mice or the values bracketing this figure which appear to be effective in humans. The present data also indicate that for regimes delivering equivalent areas under the curve in terms of serum concentration of antibody as a function of time that smaller dosages administered more frequently have a better efficacy to side effects profile than large dosages administered less frequently because the former regimes avoid the spikes in antibody concentration attendant to administering larger doses in the latter regimes. In the study in the present examples, doses were administered intravenously every 13 weeks. Although the interval for doses can be reduced to about monthly with commensurate reductions in individual doses, further increase in the frequency to weekly or biweekly (biweekly) has a high risk of noncompliance due to the inconvenience of intravenous administration, which usually requires a visit to an infusion center. However, weekly or biweekly dosing is practical by subcutaneous administration, which can easily be self-administered or administered by a caregiver without medical training. Subcutaneous delivery also results in more gradual delivery to the blood avoiding spikes in concentration. The bioavailability measured by area under the curve of antibody in plasma of subcutaneous delivery relative to intravenous delivery is about 70-100%.

[0040] Thus, preferred regimes for administering antibodies specifically binding to an N-terminal fragment of Aβ achieves an average serum concentration of administered antibody of 1-15 μg/ml in a patient. This range brackets the demonstrated effective concentrations in mice and humans allowing some margin for error in measurement and individual patient variation. The serum concentration can be determined by actual measurement or predicted from standard pharmacokinetics (e.g., WinNonline Version 4.0.1 (Pharsight Corporation, Cary, USA)) based on the amount of antibody administered, frequency of administration, route of administration and antibody half-life. The average antibody concentration in the serum is preferably within a range of 1-10, 1-5 or 2-4 μg/ml.

[0041] The present data also provide evidence that administering an antibody that specifically binds to an N-terminal fragment of Aβ in a regime sufficient to maintain a maximum serum concentration of the antibody in the patient less than about 28 μg antibody/ml serum maximizes therapeutic benefit relative to the occurrence of possible side effects, particularly vascular edema. A preferred maximum serum concentration is within a range of about 4-28 μg antibody/ml serum. The combination of maximum serum less than

about 28 μg antibody/ml serum and an average serum concentration of the antibody in the patient is below about 7 μg antibody/ml serum is particularly beneficial. See Figures 9 and 10.

[0042] The present data also provide evidence that administering an antibody that specifically binds to an N-terminal fragment of Aβ in a regime sufficient to maintain an average serum concentration of the antibody below about 7 μg antibody/ml serum maximizes therapeutic benefit relative to the occurrence of possible side effects, particularly vascular edema. A preferred average concentration is within a range of about 2-7 μg antibody/ml serum.

[0043] If the antibody is administered intravenously it is as discussed above inconvenient to have to administer it more frequently than about monthly. Preferred doses of antibody for monthly intravenous administration occur in the range of 0.1-1.0 mg/kg antibody or preferably 0.5-1.0 mg/kg antibody.

[0044] For more frequent dosing, e.g., from weekly to monthly dosing, subcutaneous administration is preferred. The doses used for subcutaneous dosing are usually in the range of 0.1 to 0.6 mg/kg or 0.01-0.35 mg/kg, preferably, 0.05-0.25 mg/kg. For weekly or biweekly dosing, the dose is preferably in the range of 0.015-0.2 mg/kg, or 0.05-0.15 mg/kg. For weekly dosing, the dose is preferably 0.05 to 0.07 mg/kg, e.g., about 0.06 mg/kg. For biweekly dosing, the dose is preferably 0.1 to 0.15 mg/kg. For monthly dosing, the dose is preferably 0.1 to 0.3 mg/kg or about 2 mg/kg. Monthly dosing includes dosing by the calendar month or lunar month (i.e., every four weeks).

[0045] Fig. 6 shows simulated steady state serum concentrations of antibody from various subcutaneous regimes assuming bioavailability of 70%. It can be seen that a dose of 0.1 mg/kg gives an average serum concentration very close to the 3.7 μg/ml found effective in mice with little peak to trough variation. Fig. 7 shows steady state concentrations of antibody following subcutaneous administration at doses of 0.05 and 0.06 mg/kg assuming 70% or 100% bioavailability. It can be seen that at 70% bioavailability, the 0.05 and 0.06 mg/kg doses lie just below and above the 3.7 μg/ml dose found effective in mice with little peak to trough variation.

[0046] The treatment regime is usually continued so that the average serum concentrations of antibody described above are maintained for at least six months or a year, and sometimes for life. The serum concentration can be measured at any time during treatment and the dose and/or frequency of administration increased if the average

concentration falls beneath a target range or the dose and/or frequency decreased if the average concentration falls above a target range.

[0047] Although determining optimal plasma concentrations of antibody is useful in determining a dosage regime or optimizing dosage in an individual patient, in practice once an effective dosage regime in terms of mg/kg or mg and frequency of administration has been determined, the same dosage regime can be used on many other patients without the need for detailed calculation or measurement of patient titers. Thus, any of the above mentioned dosages and treatment regimes can be used irrespective whether a titer is measured or predicted in a particular patient. For example, one suitable regime is intravenous administration at monthly intervals with a dose in range of 0.1-1.0 mg/kg antibody or preferably 0.5-1.0 mg/kg antibody. For subcutaneous dosing the dose used is usually in the range of 0.01-0.6 mg/kg or 0.01-0.35 mg/kg, preferably, 0.05-0.25 mg/kg. For weekly or biweekly dosing, the dose is preferably in the range of 0.015-0.2 mg/kg, or 0.05-0.15 mg/kg. For weekly dosing, the dose is preferably 0.05 to 0.07 mg/kg, e.g., 0.06 mg/kg. For biweekly dosing, the dose is preferably 0.1 to 0.15 mg/kg. For monthly dosing, the dose is preferably 0.1 to 0.3 mg/kg or 2 mg/kg.

[0048] Here as elsewhere in the application, dosages expressed in mg/kg can be converted to absolute mass dosages by multiplying by the mass of a typical patient (e.g., 70 or 75 kg) typically rounding to a whole number. Expressed in terms of absolute mass, antibodies are usually administered at a dose of 1-40 mg at a frequency of between weekly and monthly. Preferred ranges are 5-25 mg or 2.5-15 mg at a frequency of weekly to monthly. For weekly to biweekly administration, the dose is often 1-12 mg or 2.5 to 10 mg. For weekly administration, the dose is often 2.5 to 5 mg or 4-5 mg. For biweekly administration, the dose can be 7-10 mg. The mass of antibody packaged for administration in unit doses is usually round to whole number, such as 1, 5, 10, 20, 30, 40, 50, 75 or 100 mg.

[0049] The invention provides preferred dosage ranges and monitoring regimes for use in treatment of Alzheimer's disease using antibodies to Aβ. The methods are premised in part on results of a clinical trial described in the Examples. A preferred dosage range for antibodies that bind to an N-terminal fragment of Aβ is from about 0.5 to 5 mg antibody per kg patient body weight. Preferred dosages are less than 5 mg/kg. Dosages from 0.5 to 3 mg/kg, 0.5 to 1.5 mg/kg and 1.5 mg/kg are particularly preferred.

[0050] The invention also provides monitoring regimes that can assess changes in symptoms or signs of the patient following treatment. The symptoms or signs can relate to Alzheimer's disease itself and/or side effects of the treatment. The dosage of drug or its

frequency of administration can be adjusted based on the outcome of the monitoring. Alternatively or additionally, additional drugs can be administered to treat any side effects. For example, monitoring by MRI and/or FLAIR sequence imaging can be used to detect PRES or vascular edema or signs or symptoms thereof. Presence of PRES or vascular edema is an indication that the dosage should be reduced or suspended, or the interval between administration of dosages increased. Alternatively, or additionally, the patient can be administered a steroid to treat the PRES or vascular edema. After reducing or suspending dosage or increasing the interval between dosages, and/or administering the steroid, continued monitoring can indicate disappearance of PRES or vascular edema, in which case the original amount and/or interval of dosing can be resumed. Administration of the steroid may or may not be continued as a prophylactic measure at this point. As another example, monitoring of blood pressure can indicate development of hypertension. In analogous fashion, the dosage can be reduced in amount or suspended, and/or intervals between dosage increased and/or an antihypertensive administered. If and when further monitoring indicates the hypertension has disappeared, the original amount and/or interval of dosing can be resumed. Administration of antihypertensive may or may not be continued as a prophylactic measure at this point.

[0051] Prior to describing the invention, it may be helpful to an understanding thereof to set forth definitions of certain terms to be used hereinafter.

[0052] The term "immunoglobulin" or "antibody" (used interchangeably herein) refers to an antigen-binding protein having a basic four-polypeptide chain structure consisting of two heavy and two light chains, said chains being stabilized, for example, by interchain disulfide bonds, which has the ability to specifically bind antigen. Both heavy and light chains are folded into domains. The term "domain" refers to a globular region of a heavy or light chain polypeptide comprising peptide loops (*e.g.*, comprising 3 to 4 peptide loops) stabilized, for example, by β-pleated sheet and/or intrachain disulfide bond. Domains are further referred to herein as "constant" or "variable", based on the relative lack of sequence variation within the domains of various class members in the case of a "constant" domain, or the significant variation within the domains of various class members in the case of a "variable" domain. "Constant" domains on the light chain are referred to interchangeably as "light chain constant regions", "light chain constant domains", "CL" regions or "CL" domains). "Constant" domains on the heavy chain are referred to interchangeably as "heavy chain constant regions", "heavy chain constant domains", "CH" regions or "CH" domains).

"Variable" domains on the light chain are referred to interchangeably as "light chain variable regions", "light chain variable domains", "VL" regions or "VL" domains). "Variable" domains on the heavy chain are referred to interchangeably as "heavy chain constant regions", "heavy chain constant domains", "CH" regions or "CH" domains).

[0053] The term "region" refers to a part or portion of an antibody chain and includes constant or variable domains as defined herein, as well as more discrete parts or portions of said domains. For example, light chain variable domains or regions include "complementarity determining regions" or "CDRs" interspersed among "framework regions" or "FRs", as defined herein.

[0054] Immunoglobulins or antibodies can exist in monomeric or polymeric form. The term "antigen-binding fragment" refers to a polypeptide fragment of an immunoglobulin or antibody binds antigen or competes with intact antibody (*i.e.*, with the intact antibody from which they were derived) for antigen binding (*i.e.*, specific binding). The term "conformation" refers to the tertiary structure of a protein or polypeptide (*e.g.*, an antibody, antibody chain, domain or region thereof). For example, the phrase "light (or heavy) chain conformation" refers to the tertiary structure of a light (or heavy) chain variable region, and the phrase "antibody conformation" or "antibody fragment conformation" refers to the tertiary structure of an antibody or fragment thereof.

[0055] "Specific binding" of an antibody mean that the antibody exhibits appreciable affinity for antigen or a preferred epitope and, preferably, does not exhibit significant cross reactivity. "Appreciable" or preferred binding include binding with an affinity of at least 10^6, 10^7, 10^8, 10^9 M^{-1}, or 10^{10} M^{-1}. Affinities greater than 10^7 M^{-1}, preferably greater than 10^8 M^{-1} are more preferred. Values intermediate of those set forth herein are also intended to be within the scope of the present invention and a preferred binding affinity can be indicated as a range of affinities, for example, 10^6 to 10^{10} M^{-1}, preferably 10^7 to 10^{10} M^{-1}, more preferably 10^8 to 10^{10} M^{-1}. An antibody that "does not exhibit significant cross reactivity" is one that will not appreciably bind to an undesirable entity (*e.g.*, an undesirable proteinaceous entity). For example, an antibody that specifically binds to Aβ will appreciably bind Aβ but will not significantly react with non-Aβ proteins or peptides (*e.g.*, non-Aβ proteins or peptides included in plaques). An antibody specific for a preferred epitope will, for example, not significantly cross react with remote epitopes on the same protein or peptide. Specific binding can be determined according to any art-recognized means for determining such

binding. Preferably, specific binding is determined according to Scatchard analysis and/or competitive binding assays.

[0056] Binding fragments are produced by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact immunoglobulins. Binding fragments include Fab, Fab', $F(ab')_2$, Fabc, Fv, single chains, and single-chain antibodies. Other than "bispecific" or "bifunctional" immunoglobulins or antibodies, an immunoglobulin or antibody is understood to have each of its binding sites identical. A "bispecific" or "bifunctional antibody" is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. See, *e.g.*, Songsivilai & Lachmann, *Clin. Exp. Immunol.* 79:315-321 (1990); Kostelny *et al.*, *J. Immunol.* 148, 1547-1553 (1992).

[0057] The term "humanized immunoglobulin" or "humanized antibody" refers to an immunoglobulin or antibody that includes at least one humanized immunoglobulin or antibody chain (*i.e.*, at least one humanized light or heavy chain). The term "humanized immunoglobulin chain" or "humanized antibody chain" (*i.e.*, a "humanized immunoglobulin light chain" or "humanized immunoglobulin heavy chain") refers to an immunoglobulin or antibody chain (*i.e.*, a light or heavy chain, respectively) having a variable region that includes a variable framework region substantially from a human immunoglobulin or antibody and complementarity determining regions (CDRs) (*e.g.*, at least one CDR, preferably two CDRs, more preferably three CDRs) substantially from a non-human immunoglobulin or antibody, and further includes constant regions (*e.g.*, at least one constant region or portion thereof, in the case of a light chain, and preferably three constant regions in the case of a heavy chain). The term "humanized variable region" (*e.g.*, "humanized light chain variable region" or "humanized heavy chain variable region") refers to a variable region that includes a variable framework region substantially from a human immunoglobulin or antibody and complementarity determining regions (CDRs) substantially from a non-human immunoglobulin or antibody.

[0058] The phrase "substantially from a human immunoglobulin or antibody" or "substantially human" means that, when aligned to a human immunoglobulin or antibody amino sequence for comparison purposes, the region shares at least 80-90%, preferably 90-95%, more preferably 95-99% identity (*i.e.*, local sequence identity) with the human framework or constant region sequence, allowing, for example, for conservative substitutions, consensus sequence substitutions, germline substitutions, backmutations, and the like. The introduction of conservative substitutions, consensus sequence substitutions, germline

substitutions, backmutations, and the like, is often referred to as "optimization" of a humanized antibody or chain. The phrase "substantially from a non-human immunoglobulin or antibody" or "substantially non-human" means having an immunoglobulin or antibody sequence at least 80-95%, preferably 90-95%, more preferably, 96%, 97%, 98%, or 99% identical to that of a non-human organism, *e.g.*, a non-human mammal.

[0059] Accordingly, all regions or residues of a humanized immunoglobulin or antibody, or of a humanized immunoglobulin or antibody chain, except possibly the CDRs, are substantially identical to the corresponding regions or residues of one or more native human immunoglobulin sequences. The term "corresponding region" or "corresponding residue" refers to a region or residue on a second amino acid or nucleotide sequence which occupies the same (*i.e.*, equivalent) position as a region or residue on a first amino acid or nucleotide sequence, when the first and second sequences are optimally aligned for comparison purposes.

[0060] The terms "humanized immunoglobulin" or "humanized antibody" are not intended to encompass chimeric immunoglobulins or antibodies, as defined *infra*. Although humanized immunoglobulins or antibodies are chimeric in their construction (*i.e.*, comprise regions from more than one species of protein), they include additional features (*i.e.*, variable regions comprising donor CDR residues and acceptor framework residues) not found in chimeric immunoglobulins or antibodies, as defined herein.

[0061] The term "chimeric immunoglobulin" or antibody refers to an immunoglobulin or antibody whose variable regions derive from a first species and whose constant regions derive from a second species. Chimeric immunoglobulins or antibodies can be constructed, for example by genetic engineering, from immunoglobulin gene segments belonging to different species.

[0062] An "antigen" is an entity (*e.g.*, a protenaceous entity or peptide) to which an antibody specifically binds.

[0063] The term "epitope" or "antigenic determinant" refers to a site on an antigen to which an immunoglobulin or antibody (or antigen binding fragment thereof) specifically binds. Epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids in a unique spatial conformation. Methods of determining spatial conformation of epitopes include, for

example, x-ray crystallography and 2-dimensional nuclear magnetic resonance. See, *e.g.*, *Epitope Mapping Protocols in Methods in Molecular Biology,* Vol. 66, G. E. Morris, Ed. (1996).

[0064] Antibodies that recognize the same epitope can be identified in a simple immunoassay showing the ability of one antibody to block the binding of another antibody to a target antigen, *i.e.*, a competitive binding assay. Competitive binding is determined in an assay in which the immunoglobulin under test inhibits specific binding of a reference antibody to a common antigen, such as Aβ. Numerous types of competitive binding assays are known, for example: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see Stahli *et al.*, *Methods in Enzymology* 9:242 (1983)); solid phase direct biotin-avidin EIA (see Kirkland *et al.*, *J. Immunol.* 137:3614 (1986)); solid phase direct labeled assay, solid phase direct labeled sandwich assay (see Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Press (1988)); solid phase direct label RIA using I-125 label (see Morel *et al.*, *Mol. Immunol.* 25(1):7 (1988)); solid phase direct biotin-avidin EIA (Cheung *et al.*, *Virology* 176:546 (1990)); and direct labeled RIA. (Moldenhauer *et al.*, *Scand. J. Immunol.* 32:77 (1990)). Typically, such an assay involves the use of purified antigen bound to a solid surface or cells bearing either of these, an unlabeled test immunoglobulin and a labeled reference immunoglobulin. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test immunoglobulin. Usually the test immunoglobulin is present in excess. Usually, when a competing antibody is present in excess, it will inhibit specific binding of a reference antibody to a common antigen by at least 50-55%, 55-60%, 60-65%, 65-70% 70-75% or more.

[0065] An epitope is also recognized by immunologic cells, for example, B cells and/or T cells. Cellular recognition of an epitope can be determined by *in vitro* assays that measure antigen-dependent proliferation, as determined by ^{3}H-thymidine incorporation, by cytokine secretion, by antibody secretion, or by antigen-dependent killing (cytotoxic T lymphocyte assay).

[0066] Exemplary epitopes or antigenic determinants can be found within the human amyloid precursor protein (APP), but are preferably found within the Aβ peptide of APP. Multiple isoforms of APP exist, for example APP^{695}, APP^{751} and APP^{770}. Amino acids within APP are assigned numbers according to the sequence of the APP^{770} isoform (see *e.g.*, GenBank Accession No. P05067, also set forth as SEQ ID NO:38). Aβ (also referred to

herein as beta amyloid peptide and A-beta) peptide is a ~4-kDa internal fragment of 39-43 amino acids of APP (Aβ39, Aβ40, Aβ41, Aβ42 and Aβ43). Aβ40, for example, consists of residues 672-711 of APP and Aβ42 consists of residues 673-713 of APP. As a result of proteolytic processing of APP by different secretase enzymes *iv vivo* or *in situ*, Aβ is found in both a "short form", 40 amino acids in length, and a "long form", ranging from 42-43 amino acids in length. Preferred epitopes or antigenic determinants, as described herein, are located within the N-terminus of the Aβ peptide and include residues within amino acids 1-10 of Aβ, preferably from residues 1-3, 1-4, 1-5, 1-6, 1-7 or 3-7 of Aβ42. Additional referred epitopes or antigenic determinants include residues 2-4, 5, 6, 7 or 8 of Aβ, residues 3-5, 6, 7, 8 or 9 of Aβ, or residues 4-7, 8, 9 or 10 of Aβ42.

[0067] The term "amyloidogenic disease" includes any disease associated with (or caused by) the formation or deposition of insoluble amyloid fibrils. Exemplary amyloidogenic diseases include, but are not limited to systemic amyloidosis, Alzheimer's disease, mature onset diabetes, Parkinson's disease, Huntington's disease, fronto-temporal dementia, and the prion-related transmissible spongiform encephalopathies (kuru and Creutzfeldt-Jacob disease in humans and scrapie and BSE in sheep and cattle, respectively). Different amyloidogenic diseases are defined or characterized by the nature of the polypeptide component of the fibrils deposited. For example, in subjects or patients having Alzheimer's disease, β-amyloid protein (*e.g.*, wild-type, variant, or truncated β-amyloid protein) is the characterizing polypeptide component of the amyloid deposit. Accordingly, Alzheimer's disease is an example of a "disease characterized by deposits of Aβ" or a "disease associated with deposits of Aβ", *e.g.*, in the brain of a subject or patient. The terms "β-amyloid protein", "β-amyloid peptide", "β-amyloid", "Aβ" and "Aβ peptide" are used interchangeably herein.

[0068] The term "effective dose" or "effective dosage" is defined as an amount sufficient to achieve or at least partially achieve the desired effect. The term "therapeutically effective dose" is defined as an amount sufficient to cure or at least partially arrest the disease and its complications in a patient already suffering from the disease. Amounts effective for this use will depend upon the severity of the infection and the general state of the patient's own immune system.

[0069] The term "patient" includes human and other mammalian subjects that receive either prophylactic or therapeutic treatment.

[0070] "Soluble" or "dissociated" Aβ refers to non-aggregating or disaggregated Aβ polypeptide. "Insoluble" Aβ refers to aggregating Aβ polypeptide, for example, Aβ held together by noncovalent bonds. Aβ (*e.g.*, Aβ42) is believed to aggregate, at least in part, due to the presence of hydrophobic residues at the C-terminus of the peptide (part of the transmembrane domain of APP). One method to prepare soluble Aβ is to dissolve lyophilized peptide in neat DMSO with sonication. The resulting solution is centrifuged to remove any insoluble particulates.

[0071] The term "effector function" refers to an activity that resides in the Fc region of an antibody (*e.g.*, an IgG antibody) and includes, for example, the ability of the antibody to bind effector molecules such as complement and/or Fc receptors, which can control several immune functions of the antibody such as effector cell activity, lysis, complement-mediated activity, antibody clearance, and antibody half-life.

[0072] The term "effector molecule" refers to a molecule that is capable of binding to the Fc region of an antibody (*e.g.*, an IgG antibody) including, but not limited to, a complement protein or a Fc receptor.

[0073] The term "effector cell" refers to a cell capable of binding to the Fc portion of an antibody (*e.g.*, an IgG antibody) typically *via* an Fc receptor expressed on the surface of the effector cell including, but not limited to, lymphocytes, *e.g.*, antigen presenting cells and T cells.

[0074] The term "Fc region" refers to a C-terminal region of an IgG antibody, in particular, the C-terminal region of the heavy chain(s) of said IgG antibody. Although the boundaries of the Fc region of an IgG heavy chain can vary slightly, a Fc region is typically defined as spanning from about amino acid residue Cys226 to the carboxyl-terminus of an IgG heavy chain(s).

[0075] The term "Kabat numbering" unless otherwise stated, is defined as the numbering of the residues in, *e.g.*, an IgG heavy chain antibody using the EU index as in Kabat *et al.* (Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)), expressly incorporated herein by reference.

[0076] The term "Fc receptor" or "FcR" refers to a receptor that binds to the Fc region of an antibody. Typical Fc receptors which bind to an Fc region of an antibody (*e.g.*, an IgG antibody) include, but are not limited to, receptors of the FcγRI, FcγRII, and FcγRIII subclasses, including allelic variants and alternatively spliced forms of these receptors. Fc

receptors are reviewed in Ravetch and Kinet, Annu. Rev. Immunol 9:457-92 (1991); Capel *et al.*, Immunomethods 4:25-34 (1994); and de Haas *et al.*, J. Lab. Clin. Med. 126:330-41 (1995).

Immunological and Therapeutic Reagents

[0077] Immunological and therapeutic reagents of the invention comprise or consist of immunogens or antibodies, or functional or antigen binding fragments thereof, as defined herein. The basic antibody structural unit is known to comprise a tetramer of subunits. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function.

Antibodies

[0078] The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site which specifically binds (recognizes) an antigen. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and F(ab')2 fragments which can be generated by treating the antibody with an enzyme such as pepsin or produced by art-recognized recombinant engineering techniques. Aspects of the invention also relevant for the stabilization of antibodies include, for example, polyclonal and monoclonal antibodies that bind an antigen, for example a therapeutic target antigen, such as, Aβ. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of recognizing and binding to a particular epitope of a target antigen, for example, an epitope(s) of Aβ. A monoclonal antibody composition thus typically displays a single binding specificity and affinity for a particular target antigen with which it immunoreacts.

Polyclonal Antibodies

[0079] Polyclonal antibodies can be prepared as described above by immunizing a suitable subject with an immunogen. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized target antigen. If desired, the antibody molecules directed

against the target antigen can be isolated from the mammal (*e.g.*, from the blood) and further purified by well known techniques, such as protein A Sepharose chromatography to obtain the antibody, *e.g.*, IgG, fraction. At an appropriate time after immunization, *e.g.*, when the anti-antigen antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497) (see also, Brown *et al.* (1981) *J. Immunol.* 127:539-46; Brown *et al.* (1980) *J. Biol. Chem* .255:4980-83; Yeh *et al.* (1976) *Proc. Natl. Acad. Sci. USA* 76:2927-31; and Yeh *et al.* (1982) *Int. J. Cancer* 29:269-75). For the preparation of chimeric polyclonal antibodies, see Buechler *et al.* U.S. Patent No. 6,420,113.

Monoclonal Antibodies

[0080] Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating a monoclonal antibody (see, *e.g.*, G. Galfre *et al.* (1977) *Nature* 266:55052; Gefter *et al. Somatic Cell Genet.*, cited *supra*; Lerner, *Yale J. Biol. Med.*, cited *supra*; Kenneth, *Monoclonal Antibodies*, cited *supra*). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods which also would be useful. Typically, the immortal cell line (*e.g.*, a myeloma cell line) is derived from the same mammalian species as the lymphocytes. For example, murine hybridomas can be made by fusing lymphocytes from a mouse immunized with an immunogenic preparation of the present invention with an immortalized mouse cell line. Preferred immortal cell lines are mouse myeloma cell lines that are sensitive to culture medium containing hypoxanthine, aminopterin and thymidine ("HAT medium"). Any of a number of myeloma cell lines can be used as a fusion partner according to standard techniques, *e.g.*, the P3-NS1/1-Ag4-1, P3-x63-Ag8.653 or Sp2/O-Ag14 myeloma lines. These myeloma lines are available from ATCC. Typically, HAT-sensitive mouse myeloma cells are fused to mouse splenocytes using polyethylene glycol ("PEG"). Hybridoma cells resulting from the fusion are then selected using HAT medium, which kills unfused and unproductively fused myeloma cells (unfused splenocytes die after several days because they are not transformed). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind a target antigen, *e.g.*, Aβ, using a standard ELISA assay.

Recombinant Antibodies

[0081] Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with a target antigen to thereby isolate immunoglobulin library members that bind the target antigen. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP™ Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, Ladner *et al.* U.S. Patent No. 5,223,409; Kang *et al.* PCT International Publication No. WO 92/18619; Dower *et al.* PCT International Publication No. WO 91/17271; Winter *et al.* PCT International Publication WO 92/20791; Markland *et al.* PCT International Publication No. WO 92/15679; Breitling *et al.* PCT International Publication WO 93/01288; McCafferty *et al.* PCT International Publication No. WO 92/01047; Garrard *et al.* PCT International Publication No. WO 92/09690; Ladner *et al.* PCT International Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275-1281; Griffiths *et al.* (1993) *EMBO J* 12:725-734; Hawkins *et al.* (1992) *J. Mol. Biol.* 226:889-896; Clarkson *et al.* (1991) *Nature* 352:624-628; Gram *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:3576-3580; Garrad *et al.* (1991) *Bio/Technology* 9:1373-1377; Hoogenboom *et al.* (1991) *Nuc. Acid Res.* 19:4133-4137; Barbas *et al.* (1991) *Proc. Natl. Acad. Sci. USA* 88:7978-7982; and McCafferty *et al. Nature* (1990) 348:552-554.

Chimeric and Humanized Antibodies

[0082] Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention.

[0083] The term "humanized immunoglobulin" or "humanized antibody" refers to an immunoglobulin or antibody that includes at least one humanized immunoglobulin or antibody chain (*i.e.*, at least one humanized light or heavy chain). The term "humanized immunoglobulin chain" or "humanized antibody chain" (*i.e.*, a "humanized immunoglobulin light chain" or "humanized immunoglobulin heavy chain") refers to an immunoglobulin or

antibody chain (*i.e.*, a light or heavy chain, respectively) having a variable region that includes a variable framework region substantially from a human immunoglobulin or antibody and complementarity determining regions (CDRs) (*e.g.*, at least one CDR, preferably two CDRs, more preferably three CDRs) substantially from a non-human immunoglobulin or antibody, and further includes constant regions (*e.g.*, at least one constant region or portion thereof, in the case of a light chain, and three constant regions in the case of a heavy chain). The term "humanized variable region" (*e.g.*, "humanized light chain variable region" or "humanized heavy chain variable region") refers to a variable region that includes a variable framework region substantially from a human immunoglobulin or antibody and complementarity determining regions (CDRs) substantially from a non-human immunoglobulin or antibody.

[0084] The phrase "substantially from a human immunoglobulin or antibody" or "substantially human" means that, when aligned to a human immunoglobulin or antibody amino sequence for comparison purposes, the region shares at least 80-90%, 90-95%, or 95-99% identity (*i.e.*, local sequence identity) with the human framework or constant region sequence, allowing, for example, for conservative substitutions, consensus sequence substitutions, germline substitutions, backmutations, and the like. The introduction of conservative substitutions, consensus sequence substitutions, germline substitutions, backmutations, and the like, is often referred to as "optimization" of a humanized antibody or chain. The phrase "substantially from a non-human immunoglobulin or antibody" or "substantially non-human" means having an immunoglobulin or antibody sequence at least 80-95%, preferably at least 90-95%, more preferably, 96%, 97%, 98%, or 99% identical to that of a non-human organism, *e.g.*, a non-human mammal.

[0085] Accordingly, all regions or residues of a humanized immunoglobulin or antibody, or of a humanized immunoglobulin or antibody chain, except the CDRs, are substantially identical to the corresponding regions or residues of one or more native human immunoglobulin sequences. The term "corresponding region" or "corresponding residue" refers to a region or residue on a second amino acid or nucleotide sequence which occupies the same (*i.e.*, equivalent) position as a region or residue on a first amino acid or nucleotide sequence, when the first and second sequences are optimally aligned for comparison purposes.

[0086] The term "significant identity" means that two polypeptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 50-60% sequence identity, preferably at least 60-70% sequence identity, more

preferably at least 70-80% sequence identity, more preferably at least 80-90% sequence identity, even more preferably at least 90-95% sequence identity, and even more preferably at least 95% sequence identity or more (*e.g.*, 99% sequence identity or more). The term "substantial identity" means that two polypeptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 80-90% sequence identity, preferably at least 90-95% sequence identity, and more preferably at least 95% sequence identity or more (*e.g.*, 99% sequence identity or more). For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are input into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the designated program parameters.

[0087] Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith & Waterman, *Adv. Appl. Math.* 2:482 (1981), by the homology alignment algorithm of Needleman & Wunsch, *J. Mol. Biol.* 48:443 (1970), by the search for similarity method of Pearson & Lipman, *Proc. Nat'l. Acad. Sci. USA* 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by visual inspection (*see generally* Ausubel *et al.*, Current Protocols in Molecular Biology). One example of algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described in Altschul *et al., J. Mol. Biol.* 215:403 (1990). Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (publicly accessible through the National Institutes of Health NCBI internet server). Typically, default program parameters can be used to perform the sequence comparison, although customized parameters can also be used. For amino acid sequences, the BLASTP program uses as defaults a word length (W) of 3, an expectation (E) of 10, and the BLOSUM62 scoring matrix (*see* Henikoff & Henikoff, *Proc. Natl. Acad. Sci. USA* 89:10915 (1989)).

[0088] Preferably, residue positions which are not identical differ by conservative amino acid substitutions. For purposes of classifying amino acids substitutions as conservative or nonconservative, amino acids are grouped as follows: Group I (hydrophobic sidechains): leu, met, ala, val, leu, ile; Group II (neutral hydrophilic side chains): cys, ser, thr;

Group III (acidic side chains): asp, glu; Group IV (basic side chains): asn, gln, his, lys, arg; Group V (residues influencing chain orientation): gly, pro; and Group VI (aromatic side chains): trp, tyr, phe. Conservative substitutions involve substitutions between amino acids in the same class. Non-conservative substitutions constitute exchanging a member of one of these classes for a member of another.

[0089] Preferably, humanized immunoglobulins or antibodies bind antigen with an affinity that is within a factor of three, four, or five of that of the corresponding non-humanized antibody. For example, if the nonhumanized antibody has a binding affinity of 10^{-9} M, humanized antibodies will have a binding affinity of at least 3 x 10^{-8} M, 4 x 10^{-8} M, 5 x 10^{-8} M, or 10^{-9} M. When describing the binding properties of an immunoglobulin or antibody chain, the chain can be described based on its ability to "direct antigen (*e.g.*, Aβ) binding". A chain is said to "direct antigen binding" when it confers upon an intact immunoglobulin or antibody (or antigen binding fragment thereof) a specific binding property or binding affinity. A mutation (*e.g.*, a backmutation) is said to substantially affect the ability of a heavy or light chain to direct antigen binding if it affects (*e.g.*, decreases) the binding affinity of an intact immunoglobulin or antibody (or antigen binding fragment thereof) comprising said chain by at least an order of magnitude compared to that of the antibody (or antigen binding fragment thereof) comprising an equivalent chain lacking said mutation. A mutation "does not substantially affect (*e.g.*, decrease) the ability of a chain to direct antigen binding" if it affects (*e.g.*, decreases) the binding affinity of an intact immunoglobulin or antibody (or antigen binding fragment thereof) comprising said chain by only a factor of two, three, or four of that of the antibody (or antigen binding fragment thereof) comprising an equivalent chain lacking said mutation.

[0090] The term "chimeric immunoglobulin" or antibody refers to an immunoglobulin or antibody whose variable regions derive from a first species and whose constant regions derive from a second species. Chimeric immunoglobulins or antibodies can be constructed, for example by genetic engineering, from immunoglobulin gene segments belonging to different species. The terms "humanized immunoglobulin" or "humanized antibody" are not intended to encompass chimeric immunoglobulins or antibodies, as defined *infra*. Although humanized immunoglobulins or antibodies are chimeric in their construction (*i.e.*, comprise regions from more than one species of protein), they include additional features (*i.e.*, variable regions comprising donor CDR residues and acceptor framework residues) not found in chimeric immunoglobulins or antibodies, as defined herein.

[0091] Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in Robinson *et al.* International Application No. PCT/US86/02269; Akira, *et al.* European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496; Morrison *et al.* European Patent Application 173,494; Neuberger *et al.* PCT International Publication No. WO 86/01533; Cabilly *et al.* U.S. Patent No. 4,816,567; Cabilly *et al.* European Patent Application 125,023; Better *et al.* (1988) *Science* 240:1041-1043; Liu *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu *et al.* (1987) *J. Immunol.* 139:3521-3526; Sun *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura *et al.* (1987) *Canc. Res.* 47:999-1005; Wood *et al.* (1985) *Nature* 314:446-449; and Shaw *et al.* (1988) *J. Natl. Cancer Inst.* 80:1553-1559); Morrison, S. L. (1985) *Science* 229:1202-1207; Oi *et al.* (1986) *BioTechniques* 4:214; Winter U.S. Patent 5,225,539; Jones *et al.* (1986) *Nature* 321:552-525; Verhoeyan *et al.* (1988) *Science* 239:1534; and Beidler *et al.* (1988) *J. Immunol.* 141:4053-4060.

Human Antibodies from Transgenic Animals and Phage Display

[0092] Alternatively, it is now possible to produce transgenic animals (*e.g.*, mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, it has been described that the homozygous deletion of the antibody heavy-chain joining region (J_H) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array in such germ-line mutant mice results in the production of human antibodies upon antigen challenge. See, *e.g.*, U.S. Patent Nos. 6,150,584; 6,114,598; and 5,770,429.

[0093] Fully human antibodies can also be derived from phage-display libraries (Hoogenboom *et al.*, J. Mol. Biol., 227:381 (1991); Marks *et al.*, J. Mol. Biol., 222:581-597 (1991)). Chimeric polyclonal antibodies can also be obtained from phage display libraries (Buechler *et al.* U.S. Patent No. 6,420,113).

Bispecific Antibodies, Antibody Fusion Polypeptides, and Single-Chain Antibodies

[0094] Bispecific antibodies (BsAbs) are antibodies that have binding specificities for at least two different epitopes. Such antibodies can be derived from full length antibodies or antibody fragments (*e.g.* F(ab)'2 bispecific antibodies). Methods for making bispecific antibodies are known in the art. Traditional production of full length bispecific antibodies is based on the coexpression of two immunoglobulin heavy chain-light chain pairs, where the two chains have different specificities (Millstein *et al.*, Nature, 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of different antibody molecules (see, WO 93/08829 and in Traunecker *et al.*, EMBO J., 10:3655-3659 (1991)).

[0095] Bispecific antibodies also include cross-linked or "heteroconjugate" antibodies. For example, one of the antibodies in the heteroconjugate can be coupled to avidin, the other to biotin or other payload. Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in U.S. Pat. No. 4,676,980, along with a number of cross-linking techniques.

[0096] In yet another aspect, the antibody can be fused, chemically or genetically, to a payload such as a reactive, detectable, or functional moiety, for example, an immunotoxin to produce an antibody fusion polypeptide. Such payloads include, for example, immunotoxins, chemotherapeutics, and radioisotopes, all of which are well-known in the art.

[0097] Single chain antibodies are also suitable for stabilization according to the invention. The fragments comprise a heavy-chain variable domain (VH) connected to a light-chain variable domain (VL) with a linker, which allows each variable region to interface with each other and recreate the antigen binding pocket of the parent antibody from which the VL and VH regions are derived. See Gruber *et al.*, J. Immunol., 152:5368 (1994).

NANOBODIES

[0098] Nanobodies are antibody-derived therapeutic proteins that contain the properties of naturally-occurring heavy chain antibodies. Nanobodies can function as a single, relatively small, functional antigen-binding structural unit, domain or protein. The Nanobody™ technology (Ablynx N.V.) was originally developed following the discovery

that camelidae (camels and llamas) possess fully functional antibodies that lack light chains. These heavy-chain antibodies contain a single variable domain (VHH) and two constant domains (CH2 and CH3). VHH is used to distinguish them from the heavy chain variable domains that are present in conventional 4-chain antibodies (which are referred to as "VH domains"). The cloned and isolated VHH domain is a stable polypeptide harboring the full antigen-binding capacity of the original heavy-chain antibody. VHH domains and nanobodies can also be engineered into multivalent and multispecific formats. Nanobodies with an amino acid sequence that corresponds to the amino acid sequence of a naturally occurring VHH domain can be humanized, i.e. by replacing one or more amino acid residues in the amino acid sequence of the naturally occurring VHH sequence (and in particular in the framework sequences) by one or more of the amino acid residues that occur at the corresponding position(s) in a VH domain from a conventional 4-chain antibody from a human being. For details, see e.g., US 20050130266, US 20040253638, WO/2006/040153, US 20050214857, WO/2006/079372, or WO/2006/122825, each of which is incorporated herein by reference for all purposes. Antibodies against Aβ can also be produced via the Nanobody™ methods.

[0099] It is understood that any of the foregoing polypeptide molecules, alone or in combination, are suitable for preparation as stabilized formulations according to the invention.

Anti Aβ Antibodies

[00100] Generally, the formulations of the present invention include a variety of antibodies for treating amyloidogenic diseases, in particular, Alzheimer's Disease, by targeting Aβ peptide.

[00101] The terms "Aβ antibody", "anti Aβ antibody" and "anti Aβ" are used interchangeably herein to refer to an antibody that binds to one or more epitopes or antigenic determinants of the human amyloid precursor protein (APP), Aβ protein, or both. Exemplary epitopes or antigenic determinants can be found within APP, but are preferably found within the Aβ peptide of APP. Multiple isoforms of APP exist, for example APP^{695}, APP^{751} and APP^{770}. Amino acids within APP are assigned numbers according to the sequence of the APP^{770} isoform (see *e.g.*, GenBank Accession No. P05067). Examples of specific isotypes of APP which are currently known to exist in humans are the 695 amino acid polypeptide described by Kang *et. al.* (1987) *Nature* 325:733-736 which is designated as the "normal"

APP; the 751 amino acid polypeptide described by Ponte *et al.* (1988) *Nature* 331:525-527 (1988) and Tanzi *et al.* (1988) *Nature* 331:528-530; and the 770-amino acid polypeptide described by Kitaguchi *et. al.* (1988) *Nature* 331:530-532. As a result of proteolytic processing of APP by different secretase enzymes *in vivo* or *in situ*, Aβ is found in both a "short form", 40 amino acids in length, and a "long form", ranging from 42-43 amino acids in length. The short form, $A\beta_{40}$, consists of residues 672-711 of APP. The long form, *e.g.*, $A\beta_{42}$ or $A\beta_{43}$, consists of residues 672-713 or 672-714, respectively. Part of the hydrophobic domain of APP is found at the carboxy end of Aβ, and may account for the ability of Aβ to aggregate, particularly in the case of the long form. Aβ peptide can be found in, or purified from, the body fluids of humans and other mammals, *e.g.* cerebrospinal fluid, including both normal individuals and individuals suffering from amyloidogenic disorders.

[00102] The terms "β-amyloid protein", "β-amyloid peptide", "β-amyloid", "Aβ" and "Aβ peptide" are used interchangeably herein. Aβ peptide (*e.g.*, Aβ39, Aβ40, Aβ41, Aβ42 and Aβ43) is a ~4-kDa internal fragment of 39-43 amino acids of APP. Aβ40, for example, consists of residues 672-711 of APP and Aβ42 consists of residues 672-713 of APP. Aβ peptides include peptides resulting from secretase cleavage of APP and synthetic peptides having the same or essentially the same sequence as the cleavage products. Aβ peptides can be derived from a variety of sources, for example, tissues, cell lines, or body fluids (*e.g.* sera or cerebrospinal fluid). For example, an Aβ can be derived from APP-expressing cells such as Chinese hamster ovary (CHO) cells stably transfected with $APP_{717V\rightarrow F}$, as described, for example, in Walsh *et al.*, (2002), *Nature*, 416, pp 535-539. An Aβ preparation can be derived from tissue sources using methods previously described (*see*, *e.g.*, Johnson-Wood *et al.*, (1997), *Proc. Natl. Acad. Sci. USA* 94:1550). Alternatively, Aβ peptides can be synthesized using methods which are well known to those in the art. See, for example, Fields *et al.*, Synthetic Peptides: A User's Guide, ed. Grant, W.H. Freeman & Co., New York, NY, 1992, p 77). Hence, peptides can be synthesized using the automated Merrifield techniques of solid phase synthesis with the α-amino group protected by either t-Boc or F-moc chemistry using side chain protected amino acids on, for example, an Applied Biosystems Peptide Synthesizer Model 430A or 431. Longer peptide antigens can be synthesized using well known recombinant DNA techniques. For example, a polynucleotide encoding the peptide or fusion peptide can be synthesized or molecularly cloned and inserted in a suitable expression vector for the transfection and heterologous expression by a suitable host cell. Aβ peptide

also refers to related Aβ sequences that results from mutations in the Aβ region of the normal gene.

[00103] The terms "Aβ-derived diffusible ligand" and "ADDL" are small, soluble Aβ42 oligomers, predominantly trimers and tetramers but also higher-order species (See e.g., Lambert, M. P. et al. (1998) Proc. Natl. Acad. Sci. USA, vol. 95, pp. 6448-6453; Chromy, B. A. et al. (2000) Soc. Neurosci. Abstr., vol. 26, p. 1284, WO 2004/031400, each of which is incorporated by reference in its entirety for all purposes.)

[00104] The term "anti-ADDL antibody" refers to an antibody that has been generated and selected for the ability to bind ADDLs specifically, without binding to Aβ monomer or amyloid fibrils. See e.g., WO 2004/031400, incorporated by reference in its entirety for all purposes.

[00105] The term "epitope" or "antigenic determinant" refers to a site on an antigen to which an immunoglobulin or antibody (or antigen binding fragment thereof) specifically binds. Exemplary epitopes or antigenic determinants to which an Aβ antibody binds can be found within the human amyloid precursor protein (APP), but are preferably found within the Aβ peptide of APP. Exemplary epitopes or antigenic determinants within Aβ are located within the N-terminus, central region, or C-terminus of Aβ. An "N-terminal epitope", is an epitope or antigenic determinant located within the N-terminus of the Aβ peptide. Exemplary N-terminal epitopes include residues within amino acids 1-10 or 1-12 of Aβ, preferably from residues 1-3, 1-4, 1-5, 1-6, 1-7, 2-6, 2-7, 3-6, or 3-7 of Aβ42. Other exemplary N-terminal epitopes start at residues 1-3 and end at residues 7-11 of Aβ. Additional exemplary N-terminal epitopes include residues 2-4, 5, 6, 7 or 8 of Aβ, residues 3-5, 6, 7, 8 or 9 of Aβ, or residues 4-7, 8, 9 or 10 of Aβ42. "Central epitopes" are epitopes or antigenic determinants comprising residues located within the central or mid-portion of the Aβ peptide. Exemplary central epitopes include residues within amino acids 13-28 of Aβ, preferably from residues 14-27, 15-26, 16-25, 17-24, 18-23, or 19-22 of Aβ. Other exemplary central epitopes include residues within amino acids 16-24, 16-23, 16-22, 16-21, 18-21, 19-21, 19-22, 19-23, or 19-24 of Aβ. "C-terminal" epitopes or antigenic determinants are located within the C-terminus of the Aβ peptide and include residues within amino acids 33-40, 33-41, or 33-42 of Aβ. "C-terminal epitopes" are epitopes or antigenic determinants comprising residues located within the C-terminus of the Aβ peptide (*e.g.,* within about amino acids 30-40 or 30-42 of Aβ. Additional exemplary C-terminal epitopes or antigenic determinants include residues 33-40 or 33-42 of Aβ.

[00106] When an antibody is said to bind to an epitope within specified residues, such as Aβ 3-7, what is meant is that the antibody specifically binds to a polypeptide containing the specified residues (*i.e.*, Aβ 3-7 in this an example). Such an antibody does not necessarily contact every residue within Aβ 3-7. Nor does every single amino acid substitution or deletion within Aβ 3-7 necessarily significantly affect binding affinity.

[00107] In various aspects, an Aβ antibody is end-specific. As used herein, the term "end-specific" refers to an antibody which specifically binds to the N-terminal or C-terminal residues of an Aβ peptide but that does not recognize the same residues when present in a longer Aβ species comprising the residues or in APP. In various aspects, an Aβ antibody is "C-terminus-specific." As used herein, the term "C terminus-specific" means that the antibody specifically recognizes a free C-terminus of an Aβ peptide. Examples of C terminus-specific Aβ antibodies include those that: recognize an Aβ peptide ending at residue 40 but do not recognize an Aβ peptide ending at residue 41, 42, and/or 43; recognize an Aβ peptide ending at residue 42 but do not recognize an Aβ peptide ending at residue 40, 41, and/or 43; etc.

[00108] In one aspect, the Aβ antibody may be a 3D6 antibody or variant thereof, or a 10D5 antibody or variant thereof, both of which are described in U.S. Patent Publication No. 20030165496A1, U.S. Patent Publication No. 20040087777A1, International Patent Publication No. WO 02/46237A3 and International Patent Publication No. WO04/080419A2. Description of 3D6 and 10D5 antibodies can also be found, for example, in International Patent Publication No. WO02/088306A2 and International Patent Publication No. WO02/088307A2. 10D5 antibodies are also described in U.S. Patent Publication No. 20050142131. Additional 3D6 antibodies are described in U.S. Patent Application No. 11/303,478 and International Application No. PCT/US05/45614. 3D6 is a monoclonal antibody (mAb) that specifically binds to an N-terminal epitope located in the human β-amyloid peptide, specifically, residues 1-5. By comparison, 10D5 is a mAb that specifically binds to an N-terminal epitope located in the human β-amyloid peptide, specifically, residues 3-6. A cell line producing the 3D6 monoclonal antibody (RB96 3D6.32.2.4) was deposited with the American Type Culture Collection (ATCC), Manassas, VA 20108, USA on April 8, 2003 under the terms of the Budapest Treaty and has deposit number PTA-5130. A cell line producing the 10D5 monoclonal antibody (RB44 10D5.19.21) was deposited with the ATCC on April 8, 2003 under the terms of the Budapest Treaty and has deposit number PTA-5129.

[00109] Bapineuzumab means a humanized 3D6 antibody comprising a light chain having a mature variable region having the amino acid sequence designated SEQ ID NO: 1 and a heavy chain having a mature variable region having the amino acid sequence designated SEQ ID NO: 2.

Humanized 3D6 Light Chain Variable Region

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro
Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser
Leu Leu Asp Ser Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu Gln Lys
Pro Gly Gln Ser Pro Gln Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp
Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr
Cys Trp Gln Gly Thr His Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys
Val Glu Ile Lys (SEQ ID NO: 1)

Humanized 3D6 Heavy Chain Variable Region

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
Ser Asn Tyr Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
Glu Trp Val Ala Ser Ile Arg Ser Gly Gly Gly Arg Thr Tyr Tyr Ser
Asp Asn Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
Tyr Tyr Cys Val Arg Tyr Asp His Tyr Ser Gly Ser Ser Asp Tyr Trp
Gly Gln Gly Thr Leu Val Thr Val Ser Ser (SEQ ID NO: 2)

Bapineuzumab is also known as AAB-001. Figure 1 shows light and heavy chain mature variable region amino acid sequences of Bapineuzumab predicted from the expression construct DNA sequences. Amino acid sequence of the AAB-001 light and heavy chains predicted from the expression construct DNA sequences. CDR regions are underlined. Cysteines expected to form intermolecular disulfide bonds are underlined and the connectivity indicated. The N-linked glycosylation consensus site is in bold italics. The predicted heavy chain COOH-terminal lysine is shown in parenthesis.

[0100] A second version of humanized 3D6 antibody comprising a light chain having a mature variable region having the amino acid sequence designated SEQ ID NO: 3 and a heavy chain having a mature variable region having the amino acid sequence designated SEQ ID NO: 4 is shown below.

Humanized 3D6 Light Chain Variable Region
Tyr Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro
Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser
Leu Leu Asp Ser Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu Gln Lys
Pro Gly Gln Ser Pro Gln Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp
Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr
Cys Trp Gln Gly Thr His Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys
Val Glu Ile Lys (SEQ ID NO:3)

Humanized 3D6 Heavy Chain Variable Region
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
Ser Asn Tyr Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
Glu Trp Val Ala Ser Ile Arg Ser Gly Gly Gly Arg Thr Tyr Tyr Ser
Asp Asn Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu
Tyr Tyr Cys Val Arg Tyr Asp His Tyr Ser Gly Ser Ser Asp Tyr Trp
Gly Gln Gly Thr Leu Val Thr Val Ser Ser (SEQ ID NO:4)

[0101] A third version of humanized 3D6 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 5 and a heavy chain having the amino acid sequence designated SEQ ID NO: 6 is describe in US 2005/0090649 A1 published on April 28, 2005, which is incorporated herein by reference for all purposes.

Humanized 3D6 Light Chain
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
Asp Gly Lys Thr Tyr Leu Asn Trp Leu Gln Gln Arg Pro Gly Gln Ser
Pro Arg Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Trp Gln Gly
Thr His Phe Pro Arg Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys (SEQ ID NO: 5)

Humanized 3D6 Heavy Chain

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Thr Phe Ser Asn Tyr Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Ser Ile Arg Ser Gly Gly Gly Arg Thr Tyr Tyr Ser Asp Asn Val Lys Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg Tyr Asp His Tyr Ser Gly Ser Ser Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Gln Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Gln Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
Lys (SEQ ID NO: 6)

[0102] A version of humanized 10D5 antibody comprising a light chain having a mature variable region having the amino acid sequence designated SEQ ID NO: 28 and a heavy chain having a mature variable region having the amino acid sequence designated SEQ ID NO: 29 is shown below.

Humanized 10D5 Light Chain Variable Region
Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val
Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Asn Ile
Ile His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro
Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser
Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
Leu Lys Ile Lys Lys Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys
Phe Gln Gly Ser His Val Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu
Glu Leu Glu (SEQ ID NO: 28)

Humanized 10D5 Heavy Chain Variable Region
Gln Ala Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln
Ser Ser Gln Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu
Ser Thr Ser Gly Met Gly Val Ser Trp Ile Arg Gln Pro Ser Gly Lys
Gly Leu Glu Trp Leu Ala His Ile Tyr Trp Asp Asp Asp Lys Arg Tyr

Asn Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Arg
Lys Gln Val Phe Leu Lys Ile Thr Ser Val Asp Pro Ala Asp Thr Ala
Thr Tyr Tyr Cys Val Arg Arg Pro Ile Thr Pro Val Leu Val Asp Ala
Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser (SEQ ID NO: 29)

[0103] In another aspect, the antibody may be a 12B4 antibody or variant thereof, as described in U.S. Patent Publication No. 20040082762A1 and International Patent

Publication No. WO 03/077858A2. 12B4 is a mAb that specifically binds to an N-terminal epitope located in the human β-amyloid peptide, specifically, residues 3-7.

[0104] 12A11 or a chimeric or humanized or nanobody form thereof is a preferred antibody. The 12A11 antibody or a variant thereof, is described in U.S. Patent Publication No. 20050118651, U.S. Patent Publication No. 20060198851, International Patent Publication No. WO 04/108895, and International Patent Publication No. WO 06/066089, all of which are incorporated by reference in their entirety herein for all purposes. 12A11 is a mAb that specifically binds to an N-terminal epitope located in the human β-amyloid peptide, specifically, residues 3-7. A cell line producing the 12A11 monoclonal antibody was deposited at the ATCC (American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209) on December 12, 2005 and has the ATCC accession number PTA-7271.

[0105] A first version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 8 (version 1) is described in US 20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0106] Humanized 12A11 Light Chain

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln Ser Ser His Val Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys (SEQ ID NO: 7)

[0107] Humanized 12A11 Heavy Chain (version 1)

[0108] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Ser Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 8)

[0109] A second version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 9 (version 2) is described in US 20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0110] Humanized 12A11 Heavy Chain (version 2)

[0111] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Thr Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Phe Thr Ile Ser Lys Asp Thr Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID No: 9)

[0112] A third version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 10 (version 2.1) is described in US 20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0113] Humanized 12A11 Heavy Chain (version 2.1)

[0114] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Thr Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Phe Thr Ile Ser Lys Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 10)

[0115] A fourth version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 11 (version 3) is described in US 20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0116] Humanized 12A11 Heavy Chain (version 3)

[0117] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Thr Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 11)

[0118] A fifth version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 12 (version 4.1) is described in US

20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0119] Humanized 12A11 Heavy Chain (version 4.1)

[0120] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Thr Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 12)

[0121] A sixth version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 13 (version 4.2) is described in US 20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0122] Humanized 12A11 Heavy Chain (version 4.2)

[0123] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Ser Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 13)

[0124] An seventh version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 14 (version 4.3) is described in US 20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0125] Humanized 12A11 Heavy Chain (version 4.3)

[0126] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Ser Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Phe Thr Ile Ser Lys Asp Thr Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 14)

[0127] A eighth version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 15 (version 4.4) is described in US 20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0128] Humanized 12A11 Heavy Chain (version 4.4)

[0129] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Ser Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 15)

[0130] A ninth version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 16 (version 5.1) is described in US 20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0131] Humanized 12A11 Heavy Chain (version 5.1)

[0132] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Thr Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 16)

[0133] A tenth version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 17 (version 5.2) is described in US 20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0134] Humanized 12A11 Heavy Chain (version 5.2)

[0135] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Thr Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Phe Thr Ile Ser Lys Asp Thr Ser Lys Asn Thr Val Tyr Leu Gln

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 17)

[0136] An eleventh version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 18 (version 5.3) is described in US 20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0137] Humanized 12A11 Heavy Chain (version 5.3)

[0138] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Thr Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Val (SEQ ID NO: 18)

[0139] A twelfth version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 19 (version 5.4) is described in US 20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0140] Humanized 12A11 Heavy Chain (version 5.4)

[0141] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Ser Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Phe Thr Ile Ser Lys Asp Thr Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Val (SEQ ID NO: 19)

[0142] A thirteenth version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 20 (version 5.5) is described in US 20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0143] Humanized 12A11 Heavy Chain (version 5.5)

[0144] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Ser Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg

Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 20)

[0145] A fourteenth version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 21 (version 5.6) is described in US 20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0146] Humanized 12A11 Heavy Chain (version 5.6)

[0147] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Ser Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Phe Thr Ile Ser Lys Asp Thr Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 21)

[0148] A fifteenth version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 22 (version 6.1) is described in US 20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0149] Humanized 12A11 Heavy Chain (version 6.1)

[0150] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Thr Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Phe Thr Ile Ser Lys Asp Thr Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 22)

[0151] A sixteenth version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 23 (version 6.2) is described in US 20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0152] Humanized 12A11 Heavy Chain (version 6.2)

[0153] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Thr Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 23)

[0154] A seventeenth version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 24 (version 6.3) is described in US 20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0155] Humanized 12A11 Heavy Chain (version 6.3)

[0156] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Thr Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Phe Thr Ile Ser Lys Asp Thr Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 24)

[0157] A eighteenth version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 25 (version 6.4) is described in US 20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0158] Humanized 12A11 Heavy Chain (version 6.4)

[0159] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Ser Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Phe Thr Ile Ser Lys Asp Thr Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 25)

[0160] A nineteenth version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 26 (version 7) is described in US

20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0161] Humanized 12A11 Heavy Chain (version 7)

[0162] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Thr Leu Ser Thr Ser Gly Met Ser Val Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 26)

[0163] A twentieth version of the humanized 12A11 antibody comprising a light chain having the amino acid sequence designated SEQ ID NO: 7 and a heavy chain having the amino acid sequence designated SEQ ID NO: 27 (version 8) is described in US 20050118651 A1 published on June 2, 2005, which is incorporated herein by reference for all purposes.

[0164] Humanized 12A11 Heavy Chain (version 8)

[0165] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Phe Ser Gly Phe Ser Leu Ser Thr Ser Gly Met Ser Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Asn Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Thr Thr Thr Ala Asp Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 27)

[0166] In yet another aspect, the antibody may be a 6C6 antibody, or a variant thereof, as described in a U.S. Patent Publication No. US 20060165682 and International Patent Publication No. WO 06/06604 entitled "Humanized Antibodies that Recognize Beta Amyloid Peptide." 6C6 is a mAb that specifically binds to an N-terminal epitope located in the human β-amyloid peptide, specifically, residues 3-7. A cell line producing the antibody 6C6 was deposited on November 1, 2005, with the ATCC under the terms of the Budapest Treaty and assigned accession number PTA-7200.

[0167] In yet another aspect, the antibody may be a 2H3 antibody as described in U.S. Patent Publication US 20060257396. 2H3 is a mAb that specifically binds to an N-terminal epitope located in the human β-amyloid peptide, specifically, residues 2-7. A cell line producing the antibody 2H3 was deposited on December 13, 2005, with the ATCC under the terms of the Budapest Treaty and assigned accession number PTA-7267.

[0168] In yet another aspect, the antibody may be a 3A3 antibody as described in U.S. Patent Publication US 20060257396. 3A3 is a mAb that specifically binds to an N-terminal epitope located in the human β-amyloid peptide, specifically, residues 3-7. A cell line producing the antibody 3A3 was deposited on December 13, 2005, with the ATCC under the terms of the Budapest Treaty and assigned accession number PTA-7269.

[0169] In yet another aspect, the antibody may be 2B1, 1C2 or 9G8. Cell lines producing the antibodies 2B1, 1C2 and 9G8 were deposited on November 1, 2005, with the ATCC under the terms of the Budapest Treaty and were assigned accession numbers PTA-7202, PTA-7199 and PTA-7201, respectively.

[0170] Antibodies for use in the present invention may be recombinantly or synthetically produced. For example, the antibody may be produced by a recombinant cell culture process, using, e.g., CHO cells, NIH 3T3 cells, PER.C6® cells, NS0 cells, VERO cells, chick embryo fibroblasts, or BHK cells. In addition, antibodies with minor modifications that retain the primary functional property of binding Aβ peptide are contemplated by the present invention. In a particular aspect, the antibody is a humanized anti Aβ peptide 3D6 antibody that selectively binds Aβ peptide. More specifically, the humanized anti Aβ peptide 3D6 antibody is designed to specifically bind to an NH_2-terminal epitope, for example, amino acid residues 1-5, located in the human β-amyloid 1-40 or 1-42 peptide found in plaque deposits in the brain (*e.g.*, in patients suffering from Alzheimer's disease).

Prophylactic and Therapeutic Methods

[0171] The present invention is directed *inter alia* to treatment of Alzheimer's and other amyloidogenic diseases by administration of therapeutic immunological reagents (*e.g.*, humanized immunoglobulins) to specific epitopes within Aβ to a patient under conditions that generate a beneficial therapeutic response in a patient (*e.g.*, induction of phagocytosis of Aβ, reduction of plaque burden, inhibition of plaque formation, reduction of neuritic dystrophy, improving cognitive function, and/or reversing, treating or preventing cognitive decline) in the patient, for example, for the prevention or treatment of an amyloidogenic disease. The invention is also directed to use of the disclosed immunological reagents (*e.g.*, humanized immunoglobulins) in the manufacture of a medicament for the treatment or prevention of an amyloidogenic disease.

[0172] The term "treatment" as used herein, is defined as the application or administration of a therapeutic agent to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient, who has a disease, a symptom of disease or a predisposition toward a disease, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect the disease, the symptoms of disease or the predisposition toward disease.

[0173] In one aspect, the invention provides methods of preventing or treating a disease associated with amyloid deposits of Aβ in the brain of a patient. Such diseases include Alzheimer's disease, Down's syndrome and cognitive impairment. The latter can occur with or without other characteristics of an amyloidogenic disease. Some methods of the invention entail administering an effective dosage of an antibody that specifically binds to a component of an amyloid deposit to the patient. Such methods are particularly useful for preventing or treating Alzheimer's disease in human patients. Exemplary methods entail administering an effective dosage of an antibody that binds to Aβ. Preferred methods entail administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of Aβ, for example, antibodies that specifically bind to an epitope within residues 1-3 of Aβ, antibodies that specifically bind to an epitope within residues 1-4 of Aβ, antibodies that specifically bind to an epitope within residues 1-5 of Aβ, antibodies that specifically bind to an epitope within residues 1-6 of Aβ, antibodies that specifically bind to an epitope within residues 1-7 of Aβ, or antibodies that specifically bind to an epitope within residues 3-7 of Aβ. In yet another aspect, the invention features administering antibodies that bind to an epitope comprising a free N-terminal residue of Aβ. In yet another aspect, the invention features administering antibodies that bind to an epitope within residues of 1-10 of Aß wherein residue 1 and/or residue 7 of Aβ is aspartic acid. In yet another aspect, the invention features administering antibodies that specifically bind to Aβ peptide without binding to full-length amyloid precursor protein (APP). In yet another aspect, the isotype of the antibody is human IgG1.

[0174] In yet another aspect, the invention features administering antibodies that bind to an amyloid deposit in the patient and induce a clearing response against the amyloid deposit. For example, such a clearing response can be effected by Fc receptor mediated phagocytosis.

[0175] Therapeutic agents of the invention are typically substantially pure from undesired contaminant. This means that an agent is typically at least about 50% w/w

(weight/weight) purity, as well as being substantially free from interfering proteins and contaminants. Sometimes the agents are at least about 80% w/w and, more preferably at least 90 or about 95% w/w purity. However, using conventional protein purification techniques, homogeneous peptides of at least 99% w/w can be obtained.

[0176] The methods can be used on both asymptomatic patients and those currently showing symptoms of disease. The antibodies used in such methods can be human, humanized, chimeric or nonhuman antibodies, or fragments thereof (*e.g.*, antigen binding fragments) and can be monoclonal or polyclonal, as described herein. In yet another aspect, the invention features administering antibodies prepared from a human immunized with Aβ peptide, which human can be the patient to be treated with antibody.

[0177] In another aspect, the invention features administering an antibody with a pharmaceutical carrier as a pharmaceutical composition. Alternatively, the antibody can be administered to a patient by administering a polynucleotide encoding at least one antibody chain. The polynucleotide is expressed to produce the antibody chain in the patient. Optionally, the polynucleotide encodes heavy and light chains of the antibody. The polynucleotide is expressed to produce the heavy and light chains in the patient. In other aspects, the patient is monitored for level of administered antibody in the blood of the patient.

[0178] The invention thus fulfills a longstanding need for therapeutic regimes for preventing or ameliorating the neuropathology and, in some patients, the cognitive impairment associated with Alzheimer's disease.

Patients Amenable to Treatment

[0179] Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms. In the case of Alzheimer's disease, virtually anyone is at risk of suffering from Alzheimer's disease if he or she lives long enough. Therefore, the present methods can be administered prophylactically to the general population without the need for any assessment of the risk of the subject patient. The present methods are especially useful for individuals who have a known genetic risk of Alzheimer's disease. Such individuals include those having relatives who have experienced this disease, and those whose risk is determined by analysis of genetic or biochemical markers. Genetic markers of risk toward Alzheimer's disease include mutations in the APP gene, particularly mutations at position 717 and positions 670 and 671 referred to as the Hardy and Swedish mutations respectively (see Hardy, *supra*). Other markers of risk

are mutations in the presenilin genes, PS1 and PS2, and ApoE4, family history of AD, hypercholesterolemia or atherosclerosis. Individuals presently suffering from Alzheimer's disease can be recognized from characteristic dementia, as well as the presence of risk factors described above. In addition, a number of diagnostic tests are available for identifying individuals who have AD. These include measurement of CSF tau and Aβ42 levels. Elevated tau and decreased Aβ42 levels signify the presence of AD. Individuals suffering from Alzheimer's disease can also be diagnosed by ADRDA criteria as discussed in the Examples section.

[0180] In asymptomatic patients, treatment can begin at any age (*e.g.*, 10, 20, 30). Usually, however, it is not necessary to begin treatment until a patient reaches 40, 50, 60 or 70. Treatment typically entails multiple dosages over a period of time. Treatment can be monitored by assaying antibody levels over time. If the response falls, a booster dosage is indicated. In the case of potential Down's syndrome patients, treatment can begin antenatally by administering therapeutic agent to the mother or shortly after birth.

[0181] Patients amenable to treatment include patients 50 to 87 years of age, patients suffering from mild to moderate Alzheimer's disease, patients having an MMSE score of 14-26, patients having a diagnosis of probable Alzheimer's disease based on Neurological and Communicative Disorders and Stroke-Alzheimer's disease Related Disorders (NINCDS-ADRDA) criteria, and/or patients having an Rosen Modified Hachinski Ischemic score less than or equal to 4. Patients with MRI an scan consistent with the diagnosis of Alzheimer's disease, i.e., that there are no other abnormalities present on the MRI that could be attributed to other diseases, e.g. stroke, traumatic brain injury, arachnoid cysts, tumors, etc are also amendable to treatment.

[0182] The methods of the invention are particular amendable for patients that have no history or evidence of any of the following: encephalitis; clinically evident stroke; clinically significant carotid or vertebrobasilar stenosis or plaque; seizures, excluding febrile seizures in childhood; any significant autoimmune disease or disorder of the immune system; and/or clinically significant renal disorder. The methods of the invention are particular amendable for patients that have had no clinically significant infection within the 30 days before treatment commences, e.g., a chronic persistent or acute infection. The methods of the invention are particular amendable for patients that have not been treated with immunosuppressive medication (e.g., systemic corticosteroids) within 90 days before treatment commences (topical and nasal corticosteroids and inhaled corticosteroids for

asthma are permitted) or chemotherapeutic agents for malignancy within 3 years before treatment commences. The methods of the invention are also particular amendable for patients that have no clinically significant abnormality on physical, neurological, laboratory, or EKG examination (e.g. atrial fibrillation) if the abnormality could be detrimental to the patient. The methods of the invention are also particular amendable for patients that do not use anticonvulsants for seizure, anti-Parkinson's, anticoagulant (excluding the use of aspirin 325 mg/day or less), or narcotic medications.

Treatment Regimes and Dosages

[0183] In prophylactic applications, pharmaceutical compositions or medicaments are administered to a patient susceptible to, or otherwise at risk of, Alzheimer's disease in an amount sufficient to eliminate or reduce the risk, lessen the severity, or delay the outset of the disease, including biochemical, histologic and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. In therapeutic applications, compositions or medicants are administered to a patient suspected of, or already suffering from such a disease in an amount sufficient to cure, or at least partially arrest, the symptoms of the disease (biochemical, histologic and/or behavioral), including its complications and intermediate pathological phenotypes in development of the disease.

[0184] In some methods, administration of agent reduces or eliminates myocognitive impairment in patients that have not yet developed characteristic Alzheimer's pathology. An amount adequate to accomplish therapeutic or prophylactic treatment is defined as a therapeutically- or prophylactically-effective dose. In both prophylactic and therapeutic regimes, agents are usually administered in several dosages until a sufficient immune response has been achieved. The term "immune response" or "immunological response" includes the development of a humoral (antibody mediated) and/or a cellular (mediated by antigen-specific T cells or their secretion products) response directed against an antigen in a recipient subject. Such a response can be an active response, *i.e.*, induced by administration of immunogen, or a passive response, *i.e.*, induced by administration of immunoglobulin or antibody or primed T-cells.

[0185] An "immunogenic agent" or "immunogen" is capable of inducing an immunological response against itself on administration to a mammal, optionally in

conjunction with an adjuvant. Typically, the immune response is monitored and repeated dosages are given if the immune response starts to wane.

[0186] Effective doses of the compositions of the present invention, for the treatment of the above described conditions vary depending upon many different factors, including means of administration, target site, physiological state of the patient, whether the patient is human or an animal, other medications administered, and whether treatment is prophylactic or therapeutic. Usually, the patient is a human but non-human mammals including transgenic mammals can also be treated. Treatment dosages need to be titrated to optimize safety and efficacy.

[0187] For passive immunization, the dosage ranges from about 0.0001 to 100, and more usually 0.01 to 5 mg/kg of the host body weight. For example, dosage ranges can be less than 20 mg/kg body weight or 10 mg/kg body weight or within the range of 1.0 to 7 mg/kg. For passive immunization, the preferred dosage ranges from about 0.5 to less than 5 mg/kg, and more usually 0.5 to 3 mg/kg, of the host body weight. For example dosages can be less than 5 mg/kg body weight or 1.5 mg/kg body weight or within the range of 0.5 to 1.5 mg/kg, preferably at least 1.5 mg/kg. Subjects can be administered such doses daily, on alternative days, weekly or according to any other schedule determined by empirical analysis. An exemplary treatment entails administration in multiple dosages over a prolonged period, for example, of at least six months. Additional exemplary treatment regimes entail administration once per every two weeks or once a month or once every 3 to 6 months.

[0188] Exemplary passive dosage schedules include 1.5-3 mg/kg or 1.5 mg/kg every thirteen weeks. Agents of the invention are usually administered on multiple occasions. Intervals between single dosages can be weekly, monthly, every thirteen weeks, or yearly. Intervals can also be irregular as indicated by measuring blood levels of antibody to Aβ in the patient.

[0189] In some methods, dosage is adjusted to achieve a plasma antibody concentration of 1-1000 μg/ml and in some methods 25-300 μg/ml. Alternatively, antibody can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency vary depending on the half-life of the antibody in the patient. In general, human antibodies show the longest half-life, followed by humanized antibodies, chimeric antibodies, and nonhuman antibodies.

[0190] The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, compositions

containing the present antibodies or a cocktail thereof are administered to a patient not already in the disease state to enhance the patient's resistance. Such an amount is defined to be a "prophylactic effective dose." In this use, the precise amounts again depend upon the patient's state of health and general immunity, but generally range from 0.1 to 25 mg per dose, especially 0.5 to 2.5 mg per dose. A relatively low dosage is administered at relatively infrequent intervals over a long period of time. Some patients continue to receive treatment for the rest of their lives.

[0191] In therapeutic applications, a relatively high dosage (*e.g.*, from about 10 to 250 mg of antibody per dose, with dosages of from 5 to 25 mg being more commonly used) at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, and preferably until the patient shows partial or complete amelioration of symptoms of disease. Thereafter, the patent can be administered a prophylactic regime.

[0192] Therapeutic agents can be administered by parenteral, topical, intravenous, oral, subcutaneous, intraarterial, intracranial, intraperitoneal, intranasal or intramuscular means for prophylactic and/or therapeutic treatment. The most typical route of administration of a passive immunogenic agent is intravenous infusion although other routes can be equally effective. The next most common route is intramuscular injection. This type of injection is most typically performed in the arm or leg muscles. In some methods, agents are injected directly into a particular tissue where deposits have accumulated, for example intracranial injection. Intramuscular injection or intravenous infusion are preferred for administration of antibody. In some methods, particular therapeutic antibodies are injected directly into the cranium. In some methods, antibodies are administered as a sustained release composition or device, such as a Medipad™ device.

[0193] Agents of the invention can optionally be administered in combination with other agents that are at least partly effective in treatment of amyloidogenic disease. In the case of Alzheimer's and Down's syndrome, in which amyloid deposits occur in the brain, agents of the invention can also be administered in conjunction with other agents that increase passage of the agents of the invention across the blood-brain barrier.

Pharmaceutical Compositions

[0194] Agents of the invention are often administered as pharmaceutical compositions comprising an active therapeutic agent, *i.e.*, and a variety of other pharmaceutically acceptable components. See *Remington's Pharmaceutical Science* (15th ed.,

Mack Publishing Company, Easton, Pennsylvania (1980)). The preferred form depends on the intended mode of administration and therapeutic application. The compositions can also include, depending on the formulation desired, pharmaceutically-acceptable, non-toxic carriers or diluents, which are defined as vehicles commonly used to formulate pharmaceutical compositions for animal or human administration. The diluent is selected so as not to affect the biological activity of the combination. Examples of such diluents are distilled water, physiological phosphate-buffered saline, Ringer's solutions, dextrose solution, and Hank's solution. In addition, the pharmaceutical composition or formulation may also include other carriers, adjuvants, or nontoxic, nontherapeutic, nonimmunogenic stabilizers and the like.

[0195] Pharmaceutical compositions can also include large, slowly metabolized macromolecules such as proteins, polysaccharides such as chitosan, polylactic acids, polyglycolic acids and copolymers (such as latex functionalized sepharose(TM), agarose, cellulose, and the like), polymeric amino acids, amino acid copolymers, and lipid aggregates (such as oil droplets or liposomes). Additionally, these carriers can function as immunostimulating agents (*i.e.*, adjuvants).

[0196] For parenteral administration, agents of the invention can be administered as injectable dosages of a solution or suspension of the substance in a physiologically acceptable diluent with a pharmaceutical carrier that can be a sterile liquid such as water oils, saline, glycerol, or ethanol. Additionally, auxiliary substances, such as wetting or emulsifying agents, surfactants, pH buffering substances and the like can be present in compositions. Other components of pharmaceutical compositions are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, and mineral oil. In general, glycols such as propylene glycol or polyethylene glycol are preferred liquid carriers, particularly for injectable solutions. Antibodies can be administered in the form of a depot injection or implant preparation, which can be formulated in such a manner as to permit a sustained release of the active ingredient. An exemplary composition comprises monoclonal antibody at 5 mg/mL, formulated in aqueous buffer consisting of 50 mM L-histidine, 150 mM NaCl, adjusted to pH 6.0 with HCl.

[0197] Typically, compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be prepared. The preparation also can be emulsified or encapsulated in liposomes or micro particles such as polylactide, polyglycolide, or copolymer for enhanced adjuvant effect, as discussed above (see Langer, *Science* 249: 1527 (1990) and Hanes,

Advanced Drug Delivery Reviews 28:97 (1997)). The agents of this invention can be administered in the form of a depot injection or implant preparation, which can be formulated in such a manner as to permit a sustained or pulsatile release of the active ingredient.

[0198] Additional formulations suitable for other modes of administration include oral, intranasal, and pulmonary formulations, suppositories, and transdermal applications. For suppositories, binders and carriers include, for example, polyalkylene glycols or triglycerides; such suppositories can be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1%-2%. Oral formulations include excipients, such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, and magnesium carbonate. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders and contain 10%-95% of active ingredient, preferably 25%-70%.

[0199] Topical application can result in transdermal or intradermal delivery. Topical administration can be facilitated by co-administration of the agent with cholera toxin or detoxified derivatives or subunits thereof or other similar bacterial toxins (See Glenn *et al.*, *Nature* 391, 851 (1998)). Co-administration can be achieved by using the components as a mixture or as linked molecules obtained by chemical crosslinking or expression as a fusion protein.

[0200] Alternatively, transdermal delivery can be achieved using a skin path or using transferosomes (Paul *et al.*, *Eur. J. Immunol.* 25:3521 (1995); Cevc *et al.*, *Biochem. Biophys. Acta* 1368:201-15 (1998)).

Monitoring the Course of Treatment

[0201] The invention provides methods of monitoring treatment in a patient suffering from or susceptible to Alzheimer's, *i.e.*, for monitoring a course of treatment being administered to a patient. The methods can be used to monitor both therapeutic treatment on symptomatic patients and prophylactic treatment on asymptomatic patients. In particular, the methods are useful for monitoring passive immunization (*e.g.*, measuring level of administered antibody).

[0202] Some methods entail determining a baseline value, for example, of an antibody level or profile in a patient, before administering a dosage of agent, and comparing this with a value for the profile or level after treatment. A significant increase (*i.e.*, greater than the typical margin of experimental error in repeat measurements of the same sample,

expressed as one standard deviation from the mean of such measurements) in value of the level or profile signals a positive treatment outcome (*i.e.*, that administration of the agent has achieved a desired response). If the value for immune response does not change significantly, or decreases, a negative treatment outcome is indicated.

[0203] In other methods, a control value (*i.e.*, a mean and standard deviation) of level or profile is determined for a control population. Typically the individuals in the control population have not received prior treatment. Measured values of the level or profile in a patient after administering a therapeutic agent are then compared with the control value. A significant increase relative to the control value (*e.g.*, greater than one standard deviation from the mean) signals a positive or sufficient treatment outcome. A lack of significant increase or a decrease signals a negative or insufficient treatment outcome. Administration of agent is generally continued while the level is increasing relative to the control value. As before, attainment of a plateau relative to control values is an indicator that the administration of treatment can be discontinued or reduced in dosage and/or frequency.

[0204] In other methods, a control value of the level or profile (*e.g.*, a mean and standard deviation) is determined from a control population of individuals who have undergone treatment with a therapeutic agent and whose levels or profiles have reached a plateau in response to treatment. Measured values of levels or profiles in a patient are compared with the control value. If the measured level in a patient is not significantly different (*e.g.*, more than one standard deviation) from the control value, treatment can be discontinued. If the level in a patient is significantly below the control value, continued administration of agent is warranted. If the level in the patient persists below the control value, then a change in treatment may be indicated.

[0205] In other methods, a patient who is not presently receiving treatment but has undergone a previous course of treatment is monitored for antibody levels or profiles to determine whether a resumption of treatment is required. The measured level or profile in the patient can be compared with a value previously achieved in the patient after a previous course of treatment. A significant decrease relative to the previous measurement (*i.e.*, greater than a typical margin of error in repeat measurements of the same sample) is an indication that treatment can be resumed. Alternatively, the value measured in a patient can be compared with a control value (mean plus standard deviation) determined in a population of patients after undergoing a course of treatment. Alternatively, the measured value in a patient can be compared with a control value in populations of prophylactically treated patients who remain free of symptoms of disease, or populations of therapeutically treated patients who

show amelioration of disease characteristics. In all of these cases, a significant decrease relative to the control level (*i.e.*, more than a standard deviation) is an indicator that treatment should be resumed in a patient.

[0206] The tissue sample for analysis is typically blood, plasma, serum, mucous fluid or cerebrospinal fluid from the patient. The sample is analyzed, for example, for levels or profiles of antibodies to Aβ peptide, *e.g.*, levels or profiles of humanized antibodies. ELISA methods of detecting antibodies specific to Aβ are described in the Examples section. In some methods, the level or profile of an administered antibody is determined using a clearing assay, for example, in an *in vitro* phagocytosis assay, as described herein. In such methods, a tissue sample from a patient being tested is contacted with amyloid deposits (*e.g.*, from a PDAPP mouse) and phagocytic cells bearing Fc receptors. Subsequent clearing of the amyloid deposit is then monitored. The existence and extent of clearing response provides an indication of the existence and level of antibodies effective to clear Aβ in the tissue sample of the patient under test.

[0207] The antibody profile following passive immunization typically shows an immediate peak in antibody concentration followed by an exponential decay. Without a further dosage, the decay approaches pretreatment levels within a period of days to months depending on the half-life of the antibody administered. For example the half-life of some human antibodies is of the order of 20 days.

[0208] In some methods, a baseline measurement of antibody to Aβ in the patient is made before administration, a second measurement is made soon thereafter to determine the peak antibody level, and one or more further measurements are made at intervals to monitor decay of antibody levels. When the level of antibody has declined to baseline or a predetermined percentage of the peak less baseline *(e.g.*, 50%, 25% or 10%), administration of a further dosage of antibody is administered. In some methods, peak or subsequent measured levels less background are compared with reference levels previously determined to constitute a beneficial prophylactic or therapeutic treatment regime in other patients. If the measured antibody level is significantly less than a reference level (*e.g.*, less than the mean minus one standard deviation of the reference value in population of patients benefiting from treatment) administration of an additional dosage of antibody is indicated.

[0209] Additional methods include monitoring, over the course of treatment, any art-recognized physiologic symptom (*e.g.*, physical or mental symptom) routinely relied on by researchers or physicians to diagnose or monitor amyloidogenic diseases (*e.g.*, Alzheimer's

disease). For example, one can monitor cognitive impairment. The latter is a symptom of Alzheimer's disease and Down's syndrome but can also occur without other characteristics of either of these diseases. For example, cognitive impairment can be monitored by determining a patient's score on the Mini-Mental State Exam in accordance with convention throughout the course of treatment.

[0210] The patient may be monitored by at least one type of assessment selected from the group of consisting of Mini-Mental State Exam (MMSE), Alzheimer's Disease Assessment Scale - cognitive (ADAS-COG), Clinician Interview-Based Impression (CIBI), Neurological Test Battery (NTB), Disability Assessment for Dementia (DAD), Clinical Dementia Rating-sum of boxes (CDR-SOB), Neuropsychiatric Inventory (NPI), Positron Emission Tomography (PET Imaging) scan, Magnetic Resonance Imaging (MRI) scan, an EKG and measurement of blood pressure. The type of assessment may be administered on multiple occasions. For example, an MMSE may be performed before administering a dosage of the immunogenic agent, and at week 4, week 6, week 16, 6 months, and 1 year after administering the dosage of the immunogenic agent. In some patients an MMSE may be performed before administering a dosage of the immunogenic agent, and at week 6, and week 16. An MRI scan may be performed every 3 months, every 6 months, or every year.

[0211] Patients may be monitored for posterior reversible encephalopathy syndrome (PRES) or vascular edema after administration of an antibody within a range of about 0.5 mg/kg to less than 5 mg/kg, wherein the antibody specifically binds to beta amyloid peptide (Aβ) with a binding affinity of at least 10^7 M^{-1}. PRES classically consists of reversible vasogenic edema in the posterior circulation territories, however, conversion to irreversible cytoxic edema has been described. PRES is typically characterized by headache, nausea, vomiting, confusion, seizures, visual abnormalities, altered mental functioning, ataxia, frontal symptoms, parietal symptoms, stupor, and focal neurologic signs. In addition to the foregoing clinical symptoms, MRI scans or Fluid Attenuated Inversion Recovery (FLAIR) sequence imaging can be used to indicate the presence on PRES. (*See Pediatric Neurology,* 20(3):241-243; *AJNR,* 26:825-830; *NEJM,* 334(8):494-500; *Pediatr Nephrol,* 18:1161-1166; *Internal Medicine Journal,* 35:83-90; *JNNP,* 68:790-791; *AJNR,* 23:1038-1048; *Pak J Med Sci,* 21(2):149-154 and, *AJNR,* 21:1199-1209.)

[0212] Patients may be monitored for PRES or vascular edema monthly, every four months, every six months, or yearly. The patient may be monitored for at least one clinical symptom associated with PRES or vascular edema. The monitoring may comprise

performing an MRI scan. The monitoring may further comprise performing FLAIR sequence imaging. The results of the monitoring may impact the dosing regime. For example, if PRES or vascular edema is detected, dosing may be suspended or dosages may be reduced or the intervals between dosages may be increased.

[0213] Patients with PRES or vascular edema may have their blood pressure measured for hypertension. If hypertension is detected in the patient, the patient may be treated for the hypertension by administration of an antihypertensive. The antihypertensive may be selected from the group consisting of hydroclorothiazide, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II-receptor blockers (ARB), beta blockers, and calcium channel blockers. Patient with PRES or vascular edema may be treated with steroids such as dexamethasone or methyprednisol.

C. Kits

[0214] The invention further provides therapeutic products. The products comprise a glass vial and instructions. The glass vial contains a formulation comprising about 10 mg to about 250 mg of a humanized anti Aβ antibody, about 4% mannitol or about 150 mM NaCl, about 5 mM to about 10 mM histidine, and about 10 mM methionine. The instructions to monitor a patient to whom the formulation is administered for PRES and or vascular edema are included with the products. In some therapeutic products the glass vial contains a formulation comprising about 10 mg of a humanized anti Aβ antibody in about 10 mM histidine, about 10 mM methionine, about 4% mannitol, and about 0.005% polysorbate-80 (vegetable derived), with a pH of about 6.0. The instructions to monitor a patient to whom the formulation is administered for PRES or vascular edema are included with the products.

Example I. Prevention and Treatment of Human Subjects

[0215] Bapineuzumab (AAB-001) is a humanized monoclonal antibody to Aβ. The objective of this study is to determine the safety and tolerability of single doses of bapineuzumab in AD.

[0216] Methods: Randomized, double-blind, placebo-controlled single ascending dose trial of bapineuzumab infusion in patients with mild to moderate AD. Patients enrolled in the trial met all of the following criteria:

1. Diagnosis of probable Alzheimer's disease (AD) according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's disease and Related Disorders (NINCDS-ADRDA) criteria.
2. Age from 50 to 87 years, inclusive.
3. Mini-Mental Status Examination (MMSE) score of 14-26.
4. Rosen Modified Hachinski Ischemic score ≤ 4.
5. Lives at home with appropriate caregiver capable of accompanying the patient on all clinic visits, or community dwelling with caregiver capable of accompanying the patient on all clinic visits and visiting with the patient approximately 5 times per week for the duration of the study.
6. Screening visit brain magnetic resonance imaging (MRI) scan consistent with the diagnosis of AD, i.e., that there are no other abnormalities present on the MRI that can be attributed to other diseases (e.g., stroke, traumatic brain injury, arachnoid cysts, tumors, etc).
7. Surgically sterile or 2 years post-menopausal.
8. Fluent in English and evidences adequate premorbid intellectual functioning. Patient must have adequate visual and auditory abilities to perform all aspects of the cognitive and functional assessments.
9. Receiving stable doses of medication(s) for the treatment of non-excluded medical condition(s) for at least 30 days prior to screening. If a patient is taking acetylcholinesterase inhibitors or memantine, then these medication(s) must be maintained on a stable dose regimen for at least 60 days prior to screening evaluations.

Anyone of the following criteria excluded a patient from being enrolled in the trial:

1. Significant neurological disease, other than AD, that may affect cognition.
2. Current presence of a clinically significant major psychiatric disorder (e.g., major Depressive Disorder) according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), or symptom (e.g., hallucinations), that could affect the patient's ability to complete the study.
3. Current clinically significant systemic illness that is likely to result in deterioration of the patient's condition or affect the patient's safety during the study.
4. History or evidence of any of the following: encephalitis; clinically evident stroke; clinically significant carotid or vertebrobasilar stenosis or plaque; seizures,

excluding febrile seizures in childhood; any clinically significant autoimmune disease or disorder of the immune system; clinically significant renal disorder.

5. Clinically significant infection with the last 30 days (e.g., chronic persistent or acute infection).
6. Treatment with immunosuppressive medications (e.g., systemic corticosteroids) within the last 90 days (topical and nasal corticosteroids and inhaled corticosteroids for asthma are permitted) or chemotherapeutic agents for malignancy within the last 3 years.
7. Myocardial infarction within the last 2 years.
8. History of cancer within the last 5 years, with the exception of non-metastatic basal cell carcinoma and squamous cell carcinoma of the skin.
9. Other clinically significant abnormality on physical, neurological, laboratory, or ECG examination (e.g., atrial fibrillation) that could compromise the study or be detrimental to the patient.
10. Hemoglobin less than 11g/dL.
11. History of alcohol or drug dependence or abuse within the last 2 years.
12. Hamilton Psychiatric Rating Scale for Depression (HAM-D) (17-item) score >12.
13. Current use of anticonvulsants for seizure, anti-Parkinson's, anticoagulant (excluding the use of aspirin 325 mg/day or less), or narcotic medications.
14. Current use of prescription or nonprescription medication for cognitive enhancement other than cholinesterase inhibitors and memantine. Current cholinesterase inhibitor and memantine use is prohibited unless the following conditions are met: (a) maintained on a stable dose regimen for at least 60 days prior to screening; (b) patient is free of any clinically significant side effects attributable to the drug; and (c) patient and caregiver agree that, barring unforeseen circumstances, they will continue the same regimen for the duration of the trial.
15. Unless maintained on a stable dose regimen for at least 30 days prior to screening, any other medications with the potential to affect cognition other than those mentioned in #18 (including, but not limited to, anxiolytics, sedatives, hypnotics, antipsychotics, antidepressants, over-the-counter (OTC) sleeping aids, sedating anti-allergy medications, vitamin E, thyroid supplements, and vitamin B12 supplements by injection).

16. Patients who have discontinued cholinesterase inhibitors, memantine, cognitive enhancing agents, or drugs that potentially affect cognition in the 60 days prior to screening.
17. Use of an experimental medication (chemical compound) or device for AD or any other investigational medication or device for indication other than treatment for AD within 30 days prior to screening or within 5 half-lives of use of such a medication prior to screening, whichever is longer.
18. Any prior experimental treatment with AN1792, AAB-001, ACC-001, or other experimental immunotherapeutic or vaccine for AD.
19. Any prior treatment with a biologic product other than those mentioned in #18 for the treatment of AD within the last 3 years.
20. Patients who have donated blood (routine blood donation) in the 90 days prior to screening.
21. Any known hypersensitivity to any of the excipients contained in the study drug formulation.
22. Presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments of foreign objects in the eyes, skin, or body that would contraindicate a brain MRI scan.
23. Weight greater than 120 kg (264 lbs).

[0157] Results: 30 patients received bapineuzumab at doses of 0.5 mg/kg (6 active, 2 placebo) 1.5 mg/kg (6 active, 2 placebo) and 5 mg/kg (10 active, 4 placebo). 3/10 patients at 5 mg/kg developed MRI abnormalities, consisting predominantly of high signal abnormalities on FLAIR sequences, and the study did not continue past that dose. In two patients these were seen on routine surveillance scans without clinical symptoms, however a third patient experienced increased confusion. The MRI FLAIR abnormalities resolved in all three cases by 12 weeks post-dose. As part of the safety assessments MMSE was performed at baseline, week 4, week 16, 6 months and at 1 year. . Figure 2 shows the average MMSE change from baseline. Figure 3 shows the change from baseline MMSE by cohort at month 4. At week 16, the prespecified primary time point for analysis, the treatment difference relative to placebo favored the treated group at the 0.5 mg/kg dose (treatment vs. placebo difference of 2.0, p=.152) and reached statistical significance at the 1.5 mg/kg dose (treatment vs. placebo difference of 2.5, p=.047). There was no significant difference in MMSE change relative to placebo for the 5.0mg/kg group. Figure 4 shows the mean, median and standard deviation

MMSE change from baseline at month four. Figure 5 shows the results of statistical testing of the MMSE change from baseline at month four. No correlation was found between the MRI FLAIR abnormalities and the difference in MMSE change.

[0158] Plasma A-beta was elevated from baseline levels in a dose dependent fashion, peaking approximately 24 hours after the infusion. Pharmacokinetic analysis showed a half life of 22 – 28 days and was supportive of a 13-week dosing interval in multiple dosing.

[0159] Conclusion: In this small study, MMSE was statistically significantly improved compared with placebo at the 1.5mg/kg dose of bapineuzumab. The highest single infusion dose of 5mg/kg was associated with MRI FLAIR abnormalities which resolved.

[0160] Although the foregoing invention has been described in detail for purposes of clarity of understanding, it will be obvious that certain modifications may be practiced within the scope of the appended claims. All publications and patent documents cited herein, as well as text appearing in the figures, are hereby incorporated by reference in their entirety for all purposes to the same extent as if each were so individually denoted.

Example II. Pharmacokinetic Study of AAB-001

[0161] The objective of this study is to determine human pharmacokinetics (PK) after intravenous administration of AAB-001.

[0162] Methods: Randomized, double-blind, placebo-controlled multiple ascending dose trial of AAB-001 administered intravenously. 6 doses of AAB-001 were administered intravenously q13wk. There were four dose cohorts were 0.15, 0.5, 1.0 and 2.0 mg/kg.

[0163] Results: PK was predictable and dose-independent. PK – CL 0.05-0.06 mL/h/kg across all dose levels. Dose-proportional exposure. Very little accumulation with q13wk IV dosing, although quantifiable pre-infusion concentrations at all dose levels. t½ ranged from 21-34 hours. At steady-state, Cavg after 0.5 mg/kg AAB-001 (i.e., ~35 mg) ~3.3 μg/mL. See Figure 9. Cavg after 0.5 mg/kg AAB-001 of ~3.3 μg/mL is close to the 3.7 μg/mL concentration found to be efficacious in PDAPP mice. Figure 10 shows mean serum AAB-001 concentration vs. time profiles following intravenous administration of AAB-001 at doses of 0.15, 0.5, 1.0, and 2.0 mg/kg.

[0164] Plasma Aβ concentrations tend to mirror AAB-001 concentrations. At end of 13-week dosing interval, plasma Aβ levels above baseline levels and above placebo group at ≥0.5 mg/kg AAB-001 dose levels. See Figure 11. tmax ranged from 14-48 hours.

[0165] Serum anti-AAB-001 antibody levels have been undetectable in any of the samples (up to pre-Infusion #6 for the 0.5 mg/kg AAB-001 cohort).

[0166] From the foregoing it will be apparent that the invention provides for a number of uses. For example, the invention provides for the use of any of the antibodies to Aβ described above in the treatment, prophylaxis or diagnosis of amyloidogenic disease, or in the manufacture of a medicament or diagnostic composition for use in the same.

We claim:

1. A method of therapeutically treating Alzheimer's disease, comprising administering by intravenous infusion to a patient suffering from the disease a dosage of an antibody within a range of about 0.5 mg/kg to less than 5 mg/kg, wherein the antibody specifically binds to beta amyloid peptide (Aβ) with a binding affinity of at least 10^7 M^{-1}, and thereby therapeutically treat the patient.

2. A method of therapeutically treating Alzheimer's disease, comprising administering by intravenous infusion to a patient suffering from the disease a dosage of an antibody within a range of about 0.5 mg/kg to less than 5 mg/kg, wherein the antibody specifically binds to an N-terminal fragment of beta amyloid peptide (Aβ) with a binding affinity of at least 10^7 M^{-1}, and thereby therapeutically treat the patient.

3. A method of therapeutically treating Alzheimer's disease, comprising administering by intravenous infusion to a patient suffering from the disease a dosage of an antibody that specifically binds to an N-terminal fragment of beta amyloid peptide (Aβ) with a binding affinity of at least 10^7 M^{-1}, and monitoring the patient for posterior reversible encephalopathy syndrome (PRES) or vascular edema.

4. A method of therapeutically treating Alzheimer's disease, comprising administering by intravenous infusion to a patient suffering from the disease a dosage of an antibody within a range of about 0.5 mg/kg to less than 5 mg/kg, wherein the antibody specifically binds to an N-terminal fragment of beta amyloid peptide (Aβ) with a binding affinity of at least 10^7 M^{-1}, and monitoring the patient for posterior reversible encephalopathy syndrome (PRES) or vascular edema.

5. The method of claim 1, 2, 3 or 4, wherein the antibody is a humanized antibody.

6. The method of claim 5, wherein the humanized antibody is a humanized version of mouse antibody 3D6 expressed by the hybridoma deposited under ATCC under No. PTA-5130.

7. The method of claim 6, wherein the humanized antibody is bapineuzumab.

8. The method of claims 1-4 wherein the humanized antibody is a humanized version of mouse antibody 10D5 expressed by the hybridoma deposited under ATCC under No. PTA-5129.

9. The method of claim 5, wherein the humanized antibody is a humanized version of mouse antibody 12A11 expressed by the hybridoma deposited under ATCC under No. PTA-7271.

10. The method of any of claims 1-9, wherein the dosage is about 0.5 to 3 mg/kg.

11. The method of any of claims 1-9, wherein the dosage is about 0.5 to 1.5 mg/kg.

12. The method of any of claims 1-9, wherein the dosage is about 0.5 mg/kg.

13. The method of any of claims 1-9, wherein the dosage is about 1.5 mg/kg.

14. The method of any of claims 1-9, wherein the dosage is administered on multiple occasions.

15. The method of claim 14, wherein the dosage is administered every 8 to 16 weeks.

16. The method of claim 15, wherein the dosage is administered every 10 to 14 weeks.

17. The method of claim 16, wherein the dosage is administered every 13 weeks.

18. The method of claims 1, 2, 3 or 4, further comprising monitoring the patient by at least one type of assessment selected from the group of consisting of Mini-Mental State Exam (MMSE), Alzheimer's Disease Assessment Scale - cognitive (ADAS-COG), Clinician Interview-Based Impression (CIBI), Neurological Test Battery (NTB), Disability Assessment for Dementia (DAD), Clinical Dementia Rating-sum of boxes (CDR-

SOB), Neuropsychiatric Inventory (NPI), Positron Emission Tomography (PET Imaging) scan, Magnetic Resonance Imaging (MRI) scan, EKG and measurement of blood pressure.

19. The method of claim 18, wherein the assessment type is an Alzheimer's Disease Assessment Scale - cognitive (ADAS-COG).

20. The method of claim 19, wherein the ADAS-COG is administered on multiple occasions.

21. The method of claim 18, wherein the assessment type is a Neurological Test Battery (NTB).

22. The method of claim 21, wherein the NTB is administered on multiple occasions.

23. The method of claim 18, wherein the type of assessment is an MMSE.

24. The method of claim 23, wherein the MMSE is administered on multiple occasions.

25. The method of claim 24, wherein the MMSE is performed before administering the dosage, and at week 4, week 16, 6 months, and 1 year after administering the dosage.

26. The method of claim 24, wherein the MMSE score measured after administration is higher than a previously assessed MMSE score.

27. The method of claim 3 or 4, wherein the monitoring comprises performing an MRI scan.

28. The method of claim 27, wherein the monitoring further comprises performing a FLAIR (Fluid Attenuated Inversion Recovery) sequence imaging.

29. The method of claim 27, wherein the monitoring comprises identifying of at least one clinical symptom associated with PRES or vascular edema.

30. The method of claim 29, wherein the at least one clinical symptom is selected from the group consisting of headache, nausea, vomiting, confusion, seizures, visual

abnormalities, altered mental functioning, ataxia, frontal symptoms, parietal symptoms, stupor, and focal neurologic signs.

31. The method of claim 27, further comprising reducing or suspending the dosage based on an outcome of the MRI scan that is indicative of PRES or vascular edema.

32. The method of claim 28, further comprising reducing or suspending the dosage based on an outcome of the FLAIR sequence imaging that is indicative of PRES or vascular edema.

33. The method of claim 30, further comprising reducing or suspending the dosage based on an identification of at least one clinical symptom associated with PRES or vascular edema.

34. The method of claim 27, wherein the MRI scan is every 3 months, every 6 months, or every year.

35. The method of claim 28, wherein the FLAIR sequence imaging is every 3 months, every 6 months, or every year.

36. The method of any one of claims 31-33, further comprising determining presence or absence of hypertension in the patient, wherein if the patient has hypertension, the method further comprises administering an antihypertensive.

37. The method of claim 36, wherein the antihypertensive is selected from the group consisting of hydroclorothiazide, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II-receptor blockers (ARB), beta blockers, and calcium channel blockers.

38. The method of any one of claims 31-33, wherein the method further comprises administering a steroid to the patient to treat the PRES or vascular edema.

39. The method of claim 38, wherein the steroid is dexamethasone.

40. The method of claim 38, wherein the steroid is methyprednisolone.

41. The method of claim 27, further comprising reducing or suspending the dosage based on an outcome of the MRI scan and that is indicative of PRES and

identification of at least one clinical symptom associated with PRES or an outcome of the MRI scan and that is indicative of vascular edema and identification of at least one clinical symptom associated with vascular edema.

42. The method of claim 41, wherein the at least one clinical symptom is selected from the group consisting of headache, nausea, vomiting, confusion, seizures, visual abnormalities, altered mental functioning, ataxia, frontal symptoms, parietal symptoms, stupor, and focal neurologic signs.

43. The method of claim 28, further comprising reducing or suspending the dosage based on an outcome of the FLAIR sequence imaging that is indicative of PRES and identification of at least one clinical symptom associated with PRES or an outcome of the FLAIR sequencing that is indicative of vascular edema and identification of at least one clinical symptom associated with vascular edema

44. The method of claim 43, wherein the clinical symptom is selected from the group consisting of headache, nausea, vomiting, confusion, seizures, visual abnormalities, altered mental functioning, ataxia, frontal symptoms, parietal symptoms, stupor, and focal neurologic signs.

45. The method of claim 3 or 4, wherein the monitoring indicates presence of PRES or vascular edema at a first time point after administration, and absence of PRES or vascular edema at a second time point after the first point, and the patient is administered a first dosage before the monitoring indicates presence of PRES or vascular edema, a second dosage or no dosage after the monitoring detects presence of PRES or vascular edema, and a third dosage after the monitoring detects absence of PRES or vascular edema, wherein the first and third dosage are higher than the second dosage.

46. The method of claim 45, wherein the first and third dosages are the same.

47. The method of claim 3 or 4, wherein the antibody is a humanized antibody.

48. The method of claim 3 or 4, wherein the humanized antibody is a humanized version of mouse antibody 3D6 expressed by the hybridoma deposited under ATCC under No. PTA-5130.

49. The method of claim 48, wherein the humanized antibody is bapineuzumab.

50. The method of claim 3 or 4, wherein the antibody is administered at a first dosage before PRES or vascular edema is determined from the MRI scan and a second dosage after PRES or vascular edema is determined from the MRI scan, and the second dosage is less then the first dosage.

51. The method of claim 50, wherein the first dosage is 3-5 mg/kg and the second dosage is 0.5 to 3 mg/kg.

52. The method of claim 51, wherein the second dosage is half of the first dosage.

53. The method of claim 49, wherein the Bapineuzumab is administered at a first dosage before PRES or vascular edema is determined from the MRI scan and a second dosage after PRES or vascular edema is determined from the MRI scan, and the second dosage is less then the first dosage.

54. The method of claim 53, wherein the first dosage is 3-5 mg/kg and the second dosage is 0.5 to 3 mg/kg.

55. The method of claim 54, wherein the second dosage is half of the first dosage.

56. A kit for treatment of Alzheimer's disease, comprising:

a. a glass vial containing a formulation comprising:

i. about 10 mg to about 250 mg of a humanized anti Aβ antibody,

ii. about 4% mannitol or about 150 mM NaCl,iii. about 5 mM to about 10 mM histidine, and

iv. about 10 mM methionine; and

b. instructions to monitor a patient to whom the formulation is administered for PRES and or vascular edema.

57. A method of treating Alzheimer disease, comprising:

administering to a patient having the disease an antibody that specifically binds to an N-terminal fragment of Aβ in a regime sufficient to maintain an average serum concentration of the antibody in the patient in a range of 1-15 μg antibody/ml serum and thereby treating the patient.

58. The method of claim 57, wherein the average serum concentration is within a range of 1-10 μg antibody/ml serum.

59. The method of claim 57, wherein the average serum concentration is within a range of 1-5 μg antibody/ml serum.

60. The method of claim 57, wherein the average serum concentration is within a range of 2-4 μg antibody/ml serum.

61. The method of claim 57, wherein the antibody is administered intravenously.

62. The method of claim 61, wherein a dose of 0.1-1.0 mg/kg is administered monthly.

63. The method of claim 61, wherein a dose of 0.5-1.0 mg/kg is administered monthly.

64. The method of claim 57, wherein the antibody is administered subcutaneously.

65. The method of claim 57, wherein the antibody is administered at a frequency between weekly and monthly.

66. The method of claim 57, wherein the antibody is administered weekly or biweekly.

67. The method of claim 57, wherein the antibody is administered at a dose of 0.01-0.35 mg/kg.

68. The method of claim 57, wherein the antibody is administered at a dose of 0.05-0.25 mg/kg.

69. The method of claim 57, wherein the antibody is administered at a dose of 0.015-0.2 mg/kg weekly to biweekly.

70. The method of claim 57, wherein the antibody is administered at a dose of 0.05-0.15 mg/kg weekly to biweekly.

71. The method of claim 57, wherein the antibody is administered at a dose of 0.05-0.07 mg/kg weekly.

72. The method of claim 57, wherein the antibody is administered at a dose of 0.06 mg/kg weekly.

73. The method of claim 57, wherein the antibody is administered at a dose of 0.1 to 0.15 mg/kg biweekly.

74. The method of claim 57, wherein the average serum concentration of the antibody is maintained for at least six months.

75. The method of claim 57, wherein the average serum concentration of the antibody is maintained for at least one year.

76. The method of claim 57, further comprising measuring the concentration of antibody in the serum and adjusting the regime if the measured concentration falls outside the range.

77. A method of treating Alzheimer disease comprising

subcutaneously administering to a patient having the disease an antibody that specifically binds to an N-terminal fragment of Aβ, wherein the antibody is administered at a dose of 0.01-0.6 mg/kg and a frequency of between weekly and monthly.

78. The method of claim 77, wherein the antibody is administered at a dose of 0.05-0.5 mg/kg.

79. The method of claim 77, wherein the antibody is administered at a dose of 0.05-0.25 mg/kg.

80. The method of claim 77, wherein the antibody is administered at a dose of 0.015-0.2 mg/kg weekly to biweekly.

81. The method of claim 77, wherein the antibody is administered at a dose of 0.05-0.15 mg/kg weekly to biweekly.

82. The method of claim 77, wherein the antibody is administered at a dose of 0.05-0.07 mg/kg weekly.

83. The method of claim 77, wherein the antibody is administered at a dose of 0.06 mg/kg weekly.

84. The method of claim 77, wherein the antibody is administered at a dose of 0.1 to 0.15 mg/kg biweekly.

85. The method of claim 77, wherein the antibody is administered at a dose of 0.1 to 0.3 mg/kg monthly.

86. The method of claim 77, wherein the antibody is administered at a dose of 0.2 mg/kg monthly.

87. A method of treating Alzheimer disease comprising

subcutaneously administering to a patient having the disease an antibody that specifically binds to an N-terminal fragment of Aβ, wherein the antibody is administered at a dose of 1-40 mg and a frequency of between weekly and monthly.

88. The method of claim 87, wherein the antibody is administered at a dose of 5-25 mg.

89. The method of claim 87, wherein the antibody is administered at a dose of 2.5-15 mg.

90. The method of claim 87, wherein the antibody is administered at a dose of 1-12 mg weekly to biweekly.

91. The method of claim 87, wherein the antibody is administered at a dose of 2.5-10 mg weekly to biweekly.

92. The method of claim 87, wherein the antibody is administered at a dose of 2.5-5 mg weekly.

93. The method of claim 87, wherein the antibody is administered at a dose of 4-5 mg weekly.

94. The method of claim 87, wherein the antibody is administered at a dose of 7-10 mg biweekly.

95. A method of treating Alzheimer disease, comprising:

administering to a patient having the disease an antibody that specifically binds to an N-terminal fragment of Aβ in a regime sufficient to maintain a maximum serum concentration of the antibody in the patient less than about 28 μg antibody/ml serum and thereby treating the patient.

96. The method of claim 95, wherein the maximum serum concentration is within a range of about 4-28 μg antibody/ml serum.

97. The method of claim 96, wherein the maximum serum concentration is within a range of about 4-18 μg antibody/ml serum.

98. The method of any one of claims 95-97, wherein the average serum concentration of the antibody in the patient is below about 7 μg antibody/ml serum.

99. The method of claim 98, wherein the average serum concentration is within a range of about 2-7 μg antibody/ml serum.

100. The method of claim 99, wherein the average serum concentration is about 5 μg antibody/ml serum.

101. A method of treating Alzheimer disease, comprising:

administering to a patient having the disease an antibody that specifically binds to an N-terminal fragment of Aβ in a regime sufficient to maintain an average serum concentration of the antibody in the patient below about 7 μg antibody/ml serum and thereby treat the patient.

102. The method of claim 101, wherein the average serum concentration is within a range of about 2-7 μg antibody/ml serum.

103. The method of claim 102, wherein the average serum concentration is about 5 μg antibody/ml serum.

104. The method of any one of claims 95-103, wherein the antibody is administered intravenously.

105. The method of any one of claims 95-103, wherein the antibody is administered subcutaneously.

106. The method of any one of claims 95-105, wherein a dose of 0.1-1.0 mg/kg is administered monthly.

107. The method of any one of claims 95-105, wherein a dose of 0.5-1.0 mg/kg is administered monthly.

108. The method of claim 107, wherein the antibody is administered at a frequency between weekly and monthly.

109. The method of claim 108, wherein the antibody is administered weekly or biweekly.

110. The method of any one of claims 96, 97, 99 or 102, further comprising measuring the concentration of antibody in the serum and adjusting the regime if the measured concentration falls outside the range.

111. The method of claim 95 or 107, wherein the antibody is a humanized antibody.

112. The method of claim 111, wherein the humanized antibody is a humanized version of mouse antibody 3D6 expressed by the hybridoma deposited under ATCC under No. PTA-5130.

113. The method of claim 112, wherein the humanized antibody is bapineuzumab.

114. The method of claim 111, wherein the humanized antibody is a humanized version of mouse antibody 10D5 expressed by the hybridoma deposited under ATCC under No. PTA-5129.

115. The method of claim 111, wherein the humanized antibody is a humanized version of mouse antibody 12A11 expressed by the hybridoma deposited under ATCC under No. PTA-7271.

Figure 1 **Predicted Amino Acid Sequences of AAB-001 Light and Heavy Chains**

LIGHT CHAIN

1 DVVMTQSPLS LPVTPGEPAS ISCKSSQSLL DSDGKTYLNW LLQKPGQSPQ

51 RLIYLVSKLD SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCWQGTHFP

101 RTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK

151 VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE

201 VTHQGLSSPV TKSFNRGEC

Heavy Chain

HEAVY CHAIN

1 EVQLLESGGG LVQPGGSLRL SCAASGFTFS NYGMSWVRQA PGKGLEWVAS

51 IRSGGGRTYY SDNVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCVRYD

101 HYSGSSDYWG QGTLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD

151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY

201 ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK

Light Chain *Heavy Chain*

251 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQY***NS***

301 ***T***YRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV

351 YTLPPSREEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL

401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG(K)

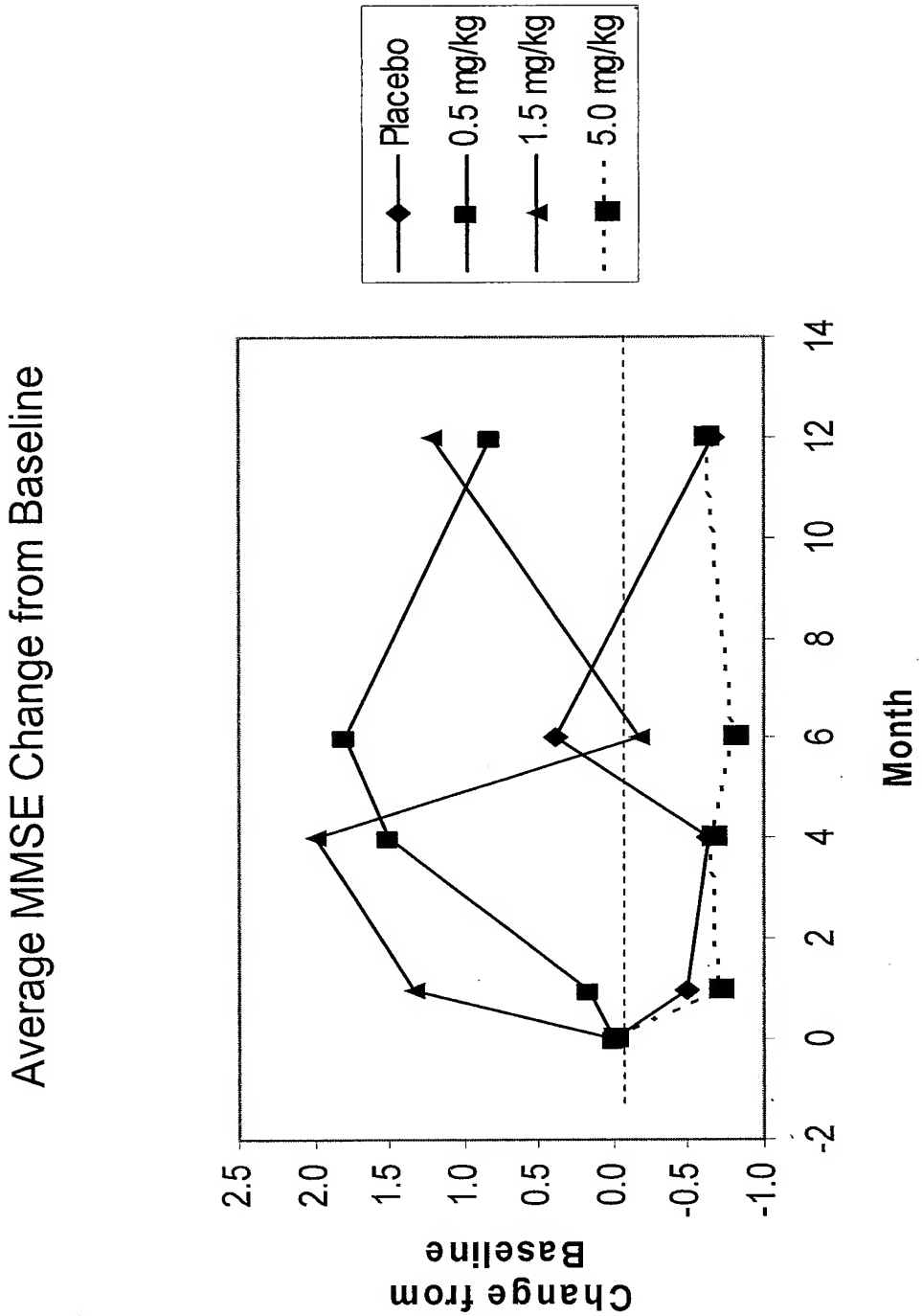

Average MMSE Change from Baseline
Placebo
0.5 mg/kg
1.5 mg/kg
5.0 mg/kg
Change from Baseline
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-2
0
2
4
6
8
10
12
14
Month

Fig. 2

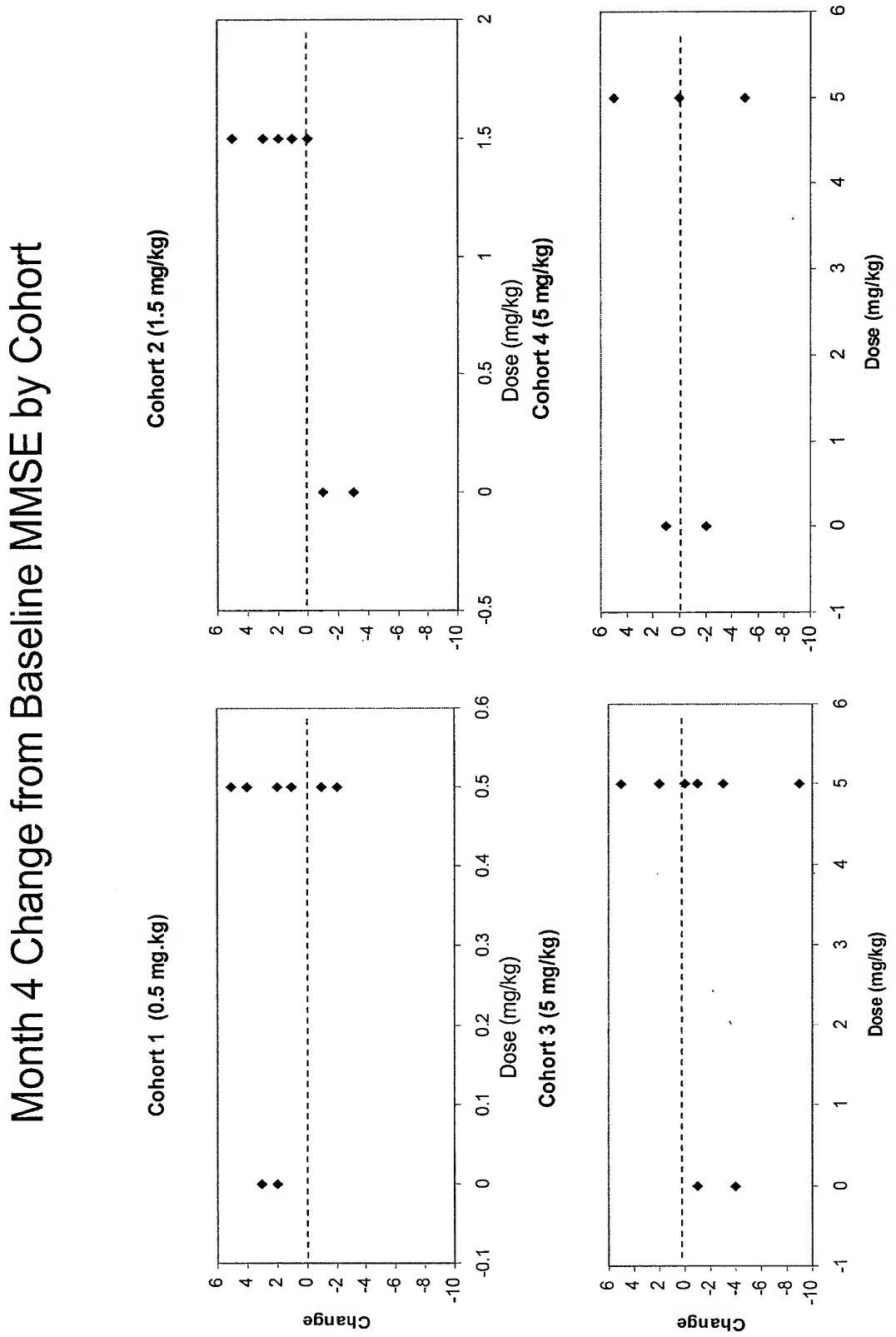

Month 4 Change from Baseline MMSE by Cohort
Cohort 1 (0.5 mg.kg)
Cohort 2 (1.5 mg/kg)
Cohort 3 (5 mg/kg)
Cohort 4 (5 mg/kg)
Change
Dose (mg/kg)

Fig. 3

Month 4 MMSE Change from Baseline

Dose	n	Mean	Median	SD
Placebo	8	-0.63	-1.0	2.446
0.5 mg/kg	6	1.50	1.5	2.739
1.5 mg/kg	6	2.00	1.5	1.789
5.0 mg/kg	9	-0.67	0.0	4.555

Fig. 4

Statistical Testing: Month 4 MMSE Change from Baseline

- Primary SAP Specified Analysis:
  - Test of linear trend: p=0.3840
- Additional Analyses:

Method	Placebo (n=8) vs. 0.5 mg/kg (n=6)	Placebo (n=8) vs. 1.5 mg/kg (n=6)	Placebo (n=8) vs. 0.5 +1.5 mg/kg (n=12)
Unadjusted ANCOVA	0.152	0.047	0.037
ANCOVA adjusted for baseline MMSE	0.199	0.018	0.0499
Mann-Whitney Test (non-parametric)	0.172	0.069	0.057

Fig. 5

Figure 6 Simulated steady state prediction across a range of doses (0.05-0.25 mg/kg) of SQ AAB-001 at projected bioavailability level of 70% (biweekly dosing)

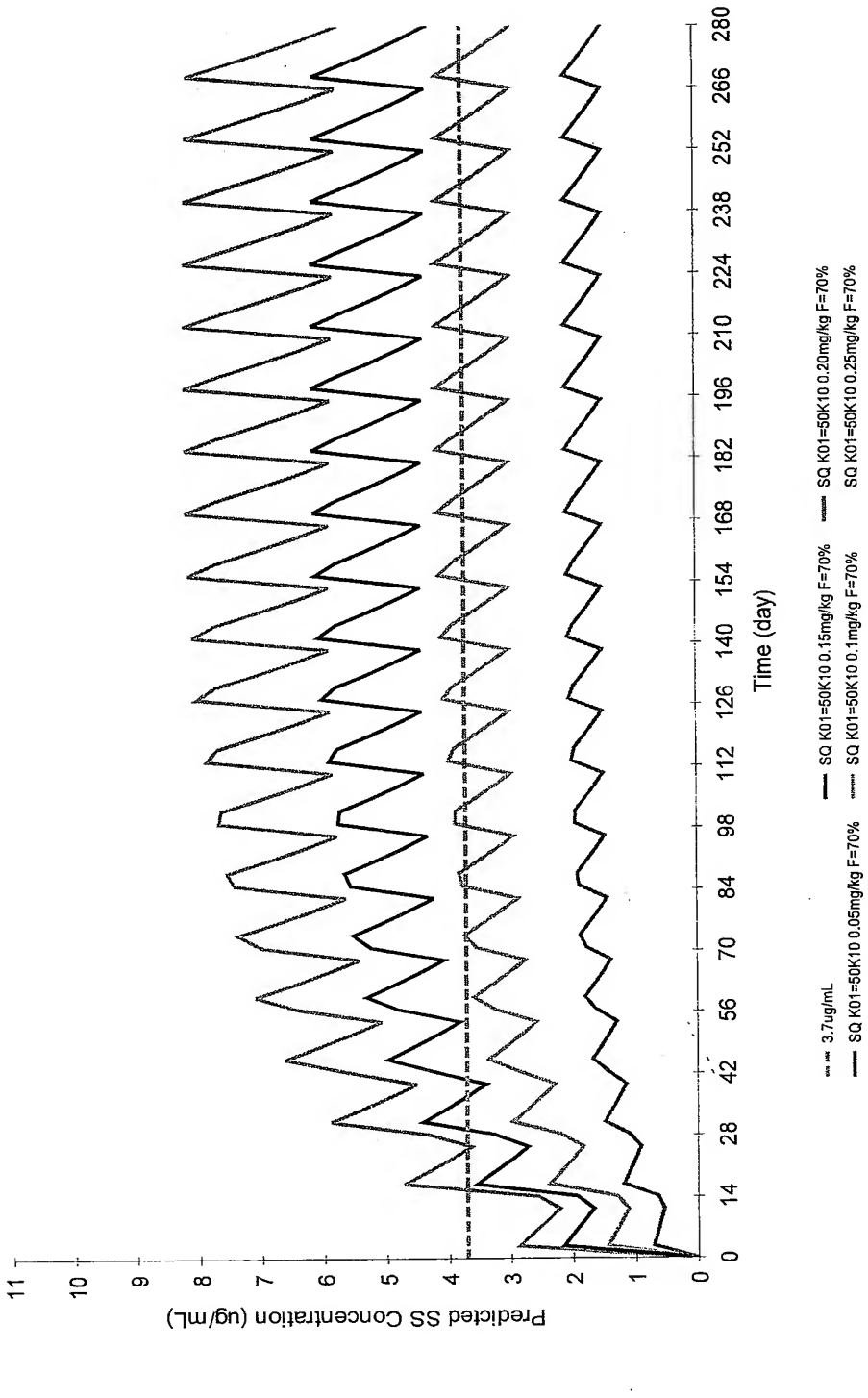


Figure 7 Simulated steady state prediction across a range of doses (0.05-0.06 mg/kg) of SQ AAB-001 at projected bioavailability level of 100% and 70% (weekly dosing)

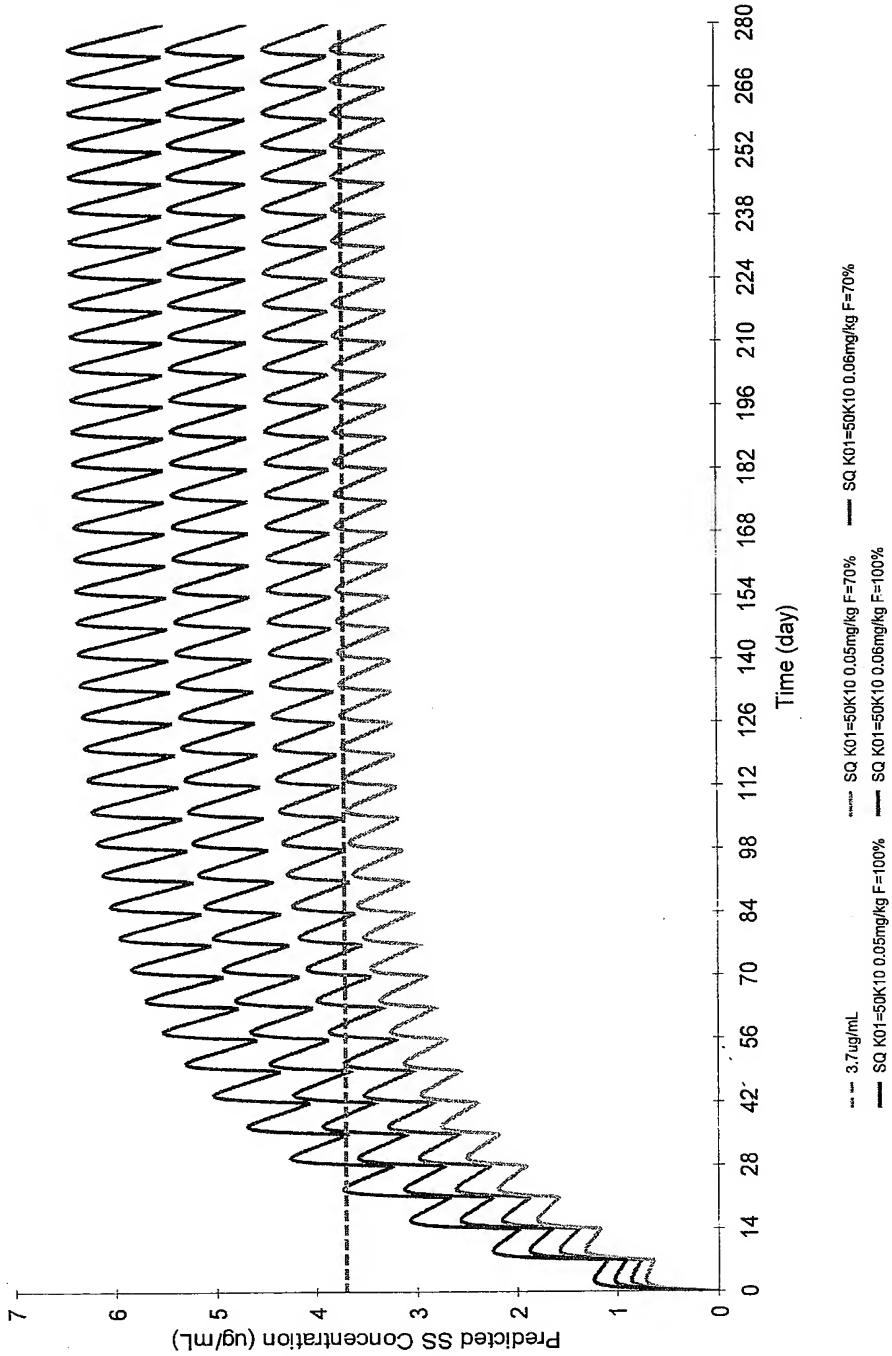


Figure 8: Study 201: Plasma Aβ Levels (PD Effect)

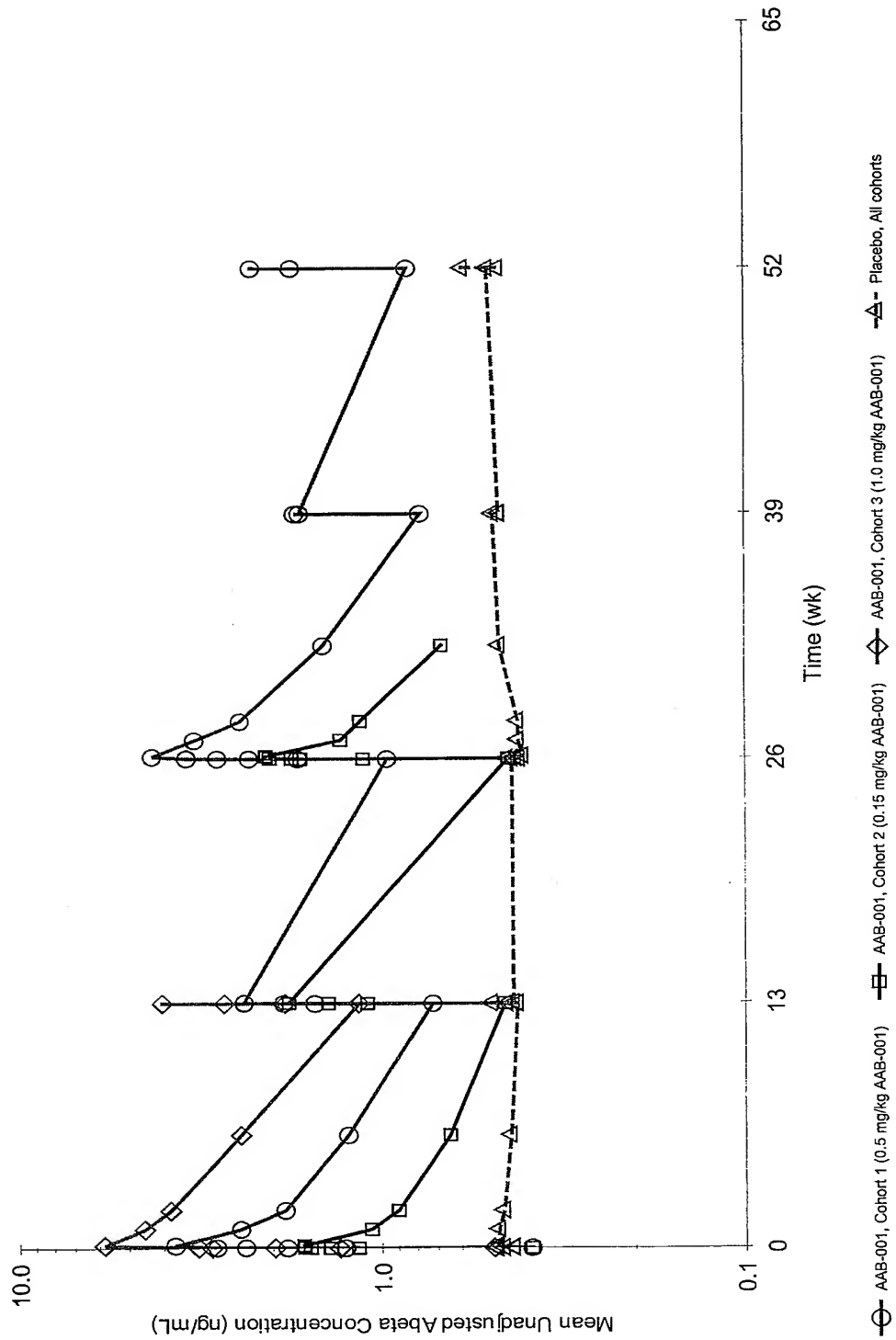


Figure 9
Study 201: Mean Serum AAB-001 Concentration vs. Time Profiles after IV Administration

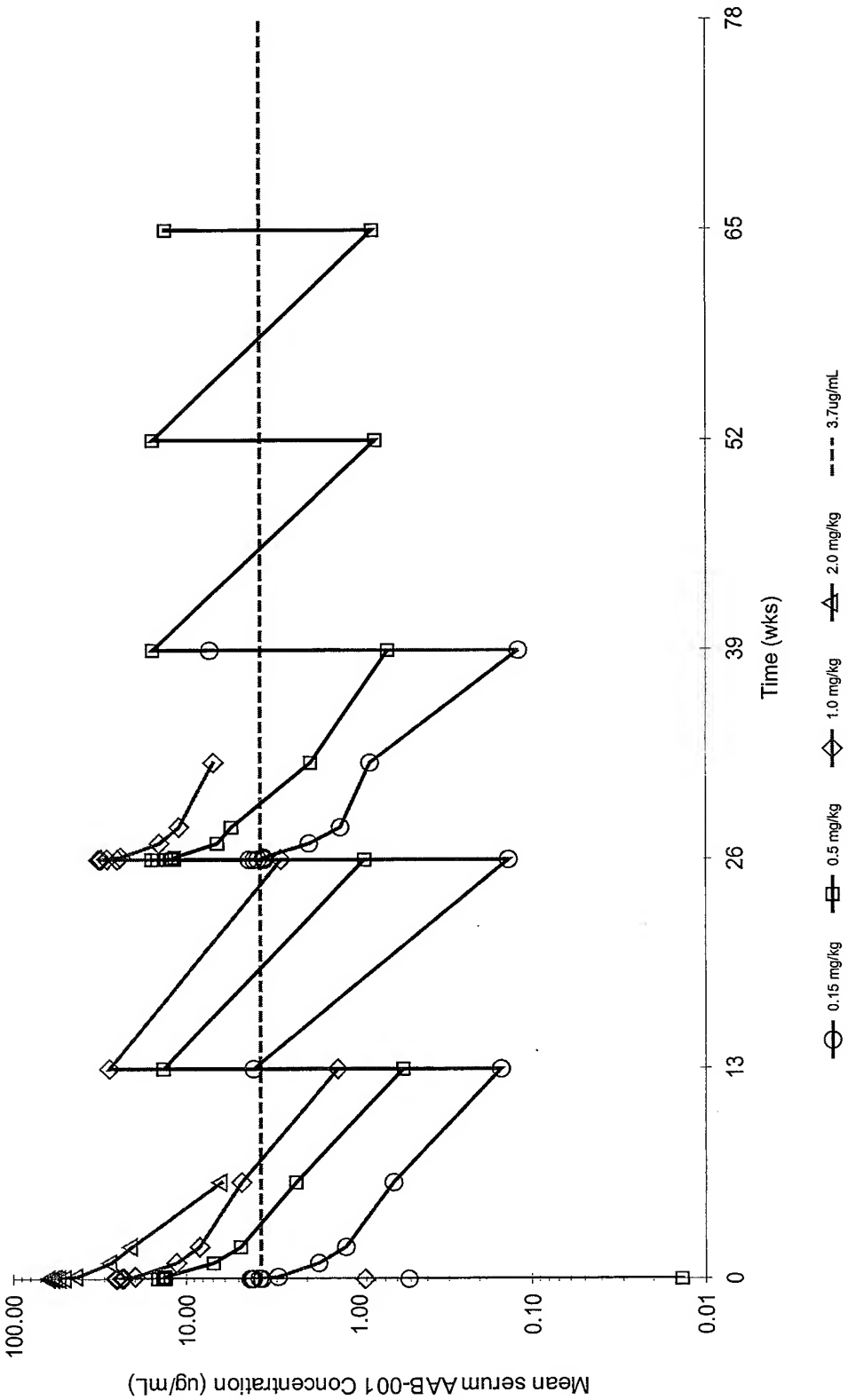


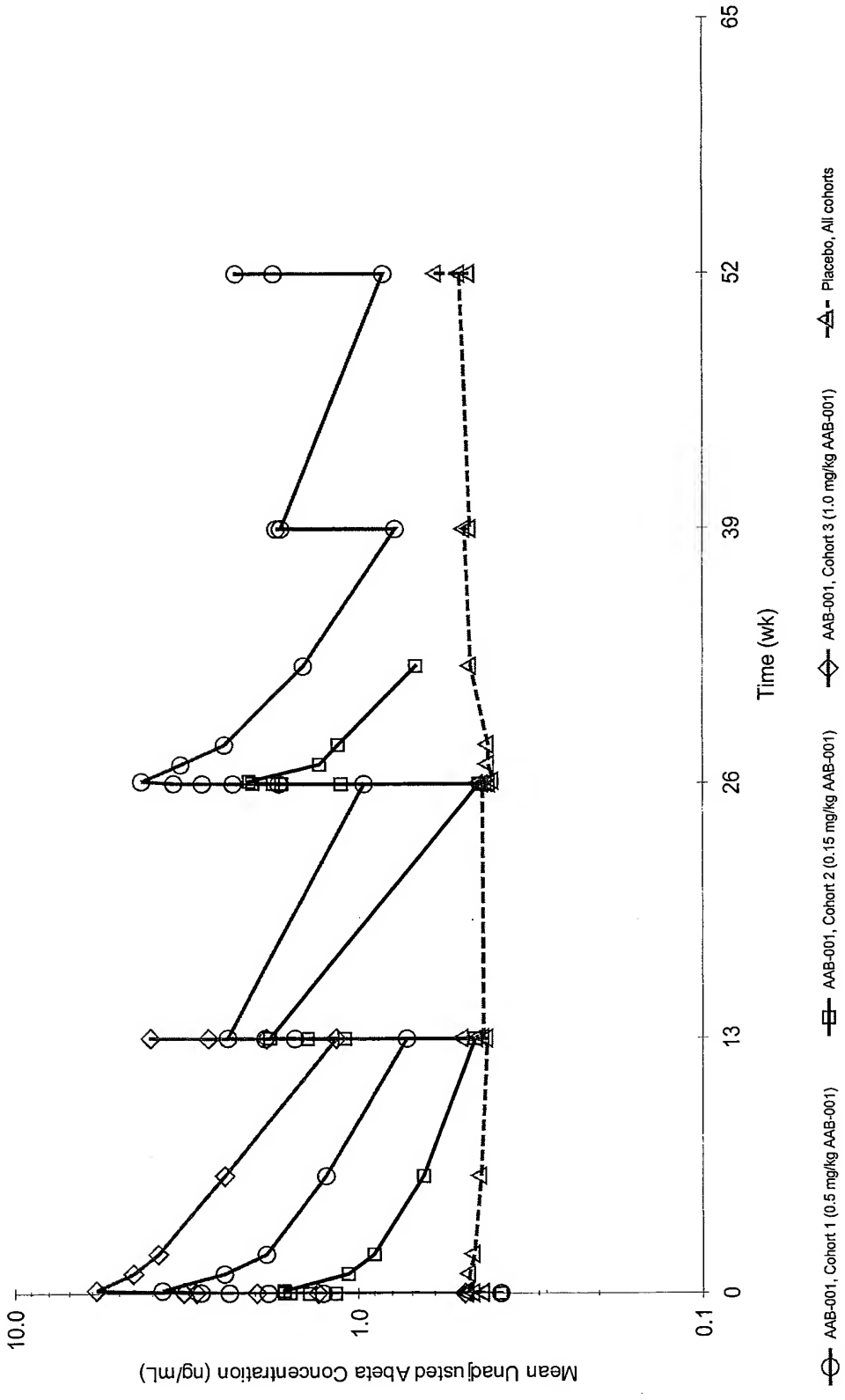
Figure 10

Study 201: IV AAB-001 PK Parameters

INFUSION #1									
AAB-001 Dose	**Parameter**	**C_{max} (µg/mL)**			**t_{max} (h)**	**AUC_{inf} (µg.h/mL)**	**CL (mL/h/kg)**	**Vz (mL/kg)**	**$t_{1/2}$ (days)**
0.15 mg/kg (Cohort 2)	n Mean (SD)	6 4.60 (0.61)			6 1.5 (median)	6 1897 (255)	6 0.06 (0.01)	6 56.49 (22.27)	6 26.65 (9.07)
0.5 mg/kg (Cohort 1)	n Mean (SD)	6 17.20 (5.34)			6 1.75 (median)	6 7578 (1717)	6 0.05 (0.01)	6 45.87 (8.44)	6 26.26 (7.07)
1.0 mg/kg (Cohort 3)	n Mean (SD)	6 28.04 (4.59)			6 1.99 (median)	6 14135 (4373)	6 0.06 (0.02)	6 58.13 (11.43)	6 28.50 (6.07)
2.0 mg/kg (Cohort 4)	n Mean (SD)	3 63.17 (11.28)			3 1.99 (median)	NE	NE	NE	NE
INFUSION #3									
AAB-001 Dose	**Parameter**	**C_{max} (µg/mL)**	**C_{avg} (µg/mL)**	**C_{min} (µg/mL)**	**t_{max} (h)**	**AUC_{tau} (µg.h/mL)**	**CL (mL/h/kg)**	**Vz (mL/kg)**	**$t_{1/2}$ (days)**
0.15 mg/kg (Cohort 2)	n Mean (SD)	6 4.42 (0.93)	6 1.08 (0.24)	6 0.11 (0.04)	6 1.00 (median)	6 2364 (517)	6 0.05 (0.02)	6 34.65 (13.31)	6 21.13 (2.87)
0.5 mg/kg (Cohort 1)	n Mean (SD)	4 17.04 (5.09)	4 3.28 (1.26)	4 0.76 (0.52)	4 1.24 (median)	4 7164 (2755)	4 0.05 (0.02)	4 42.42 (13.67)	4 23.75 (8.81)
1.0 mg/kg (Cohort 3)	n Mean (SD)	4 32.13 (2.36)	4 5.65 (2.79)	3 2.82 (1.17)	4 1.73 (median)	2 16869 (5319)	2 0.05 (0.02)	2 50.40 (9.48)	2 34.01 (8.68)

NE = Not evaluable

Figure 11
Study 201: Plasma Aβ Levels (PD Effect)



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/80370

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/00 (2008.04)
USPC - 514/2
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/2
(text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(PGPB,USPT,USOC,EPAB,JPAB); Google; PubMed
Search terms: alzheimer's, antibody, bapineuzumab, PTA-5130, PTA-7271, posterior reversible encephalopathy syndrome, MMSE, NTB, ADAS, FLAIR, a.beta., beta amyloid

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 2006/0193850 A1 (WARNE et al.) 31 August 2006 (31.08.2006) para [0010], [0033], [0035]-[0036], [0050], [0059], [0098], [0127], [0129], [0172]-[0173]	1-2, 5-7, 57-103 --- 3-4, 9, 18-35, 41-56
Y	US 2007/0082367 A1 (GODAVARTI et al.) 12 April 2007 (12.07.2007) para [0137]-[0138]	9
Y	US 2006/0121038 A9 (SCHENK et al.) 8 June 2006 (08.06.2006) para [0008], [0408]-[0409]	18-26
Y	MAVRAGANI et al. A case of reversible posterior leucoencephalopathy syndrome after rituximab infusion. Rheumatology (Oxford). November 2004 (11.2004), Vol. 43, No. 11, pages 1450-1451; pg 1450, para 1, 6, 8; pg 1451, para 1, 3	3-4, 27-35, 41-56
Y	ALLEN et al. Reversible posterior leukoencephalopathy syndrome after bevacizumab/FOLFIRI regimen for metastatic colon cancer. Arch. Neurol. October 2006 (10.2006), Vol. 63, No. 10, pages 1475-1478; abstract; pg 1477, para 3	3-4, 27-35, 41-56
Y	US 2006/0234912 A1 (WANG et al.) 19 October 2006 (19.10.2006) para [0159]	21-22
Y	US 2006/0182321 A1 (HU et al.) 17 August 2006 (17.08.2006) para [0002], [0005], [0009], [0042]	28, 32, 35, 43-44

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 December 2008 (22.12.2008)	22 JAN 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/80370

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 8, 10-17, 36-40, 104-115
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.